Catalysis

Novel Access to Known and Unknown Thiourea Catalyst via a Multicomponent-Reaction Approach

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Thioureas are frequently used in organocatalysis and typically rely on 3,5-bis(trifluoromethyl) phenyl moieties motifs to enhance their catalytic activity. In this work, these common motifs were replaced with tailorable functional groups, such as ester or sulfone aryls, applying elemental sulfur in a multicomponent reaction (MCR) strategy for the first time for thiourea catalyst synthesis. First, several thioureas bearing aryl, benzylic or aliphatic moieties were synthesized and tested for their hydrogen bonding strength by evaluating thiourea phosphine oxide complexes via ^{31}P NMR and their catalytic activity in an Ugi four-component reaction (U-4CR). Finally, ester and sulfone aryl thioureas were tested in the aminolysis of propylene carbonate, leading to conversions similar to those previously reported in the literature using the 3,5-bis (trifluoromethyl)phenyl moiety, proving that these groups are suitable alternatives for the trifluoromethyl group.

Introduction

N, *N'*-Monosubstituted thiourea compounds are frequently applied to catalyze a broad range of reactions, including Diels-Alder reactions,[1–3] Michael additions,[4–8] Henry reaction,[9,10] acetalization,[11–13] Mannich-type reactions,[14–19] as well as ring-opening polymerizations (ROP)[20–22] in a mild and often asymmetric fashion. These organocatalysts typically act as non-covalent Lewis acid–like catalysts due to their ability to form double hydrogen bonding in a planar geometry.[1,23–25] Their catalytic interactions arise via several mechanisms, for instance by direct activation of the electrophile by hydrogen bonding,[24–26] indirect activation by anion-binding of the substrate,[27–30] or by increasing the catalysts Brønsted acidity by anion stabilization (the thiourea compound acts as co-catalyst).[14,17,31,32] Recently, a few cases reported that thioureas can also act as Brønsted acids in a catalytic fashion.[33,34]

In general, electron-poor aryl moieties adjacent to the thiourea nitrogen enhance the hydrogen donor ability and thus the catalytic activity.[2,35] Most often, 3,5-bis(trifluoromethyl) phenyl[35] or other fluoro substituted aryl moieties[1,2,19,34,36] are used at one or both sites of the thiourea group for this task. Nevertheless, several moieties have been reported that also lead to a significant increase of the catalytic activity of thioureas using electron-withdrawing groups, such as aromatic acetyl or sulfone[37,38] as well as sulfoxide moieties,[10] directly attached to the thiourea group. Furthermore, ionic interactions, such as protonated[39] or methylated pyridine moieties,[3] or intramolecular hydrogen bonding[18,19] have been reported to influence the catalytic activity. Despite the fact that several alternative motifs are established in literature, mainly the 3,5-bis(trifluoromethyl) phenyl motif is used.

This work has two main aims: (i) to replace the commonly used 3,5-bis(trifluoromethyl) phenyl motifs by surrogates that perform similarly or exhibit improved catalytic activity and furthermore (ii) to introduce a new and simplified synthesis strategy for thiourea catalysts. Thus, in contrast to the typically applied thiourea catalysts synthesis routes involving thiophosgene,[40–42] its surrogates[34,43–47] or other toxic compounds,[48,49] a multicomponent reaction (MCR) approach is investigated herein in order to decrease the overall toxicological impact and at the same time provide a straightforward and structurally versatile access to the desired catalysts. Our approach is based on a report by Al-Mourabit *et al.*,[50] who extended the synthesis protocol of Lipp *et al.*[51] and reported the synthesis of thioureas from aliphatic amines, isocyanides and elemental sulfur in excellent yields at ambient to moderate temperature. Apart from offering an atom efficiency of 100%, elemental sulfur, which is an abundant non-toxic waste product of the petroleum industry (almost 80 million metric tons in 2019[52]) and a significant environmental burden,[53,54] can be used directly in this approach. Thus, highly toxic reagents and substrates were avoided, since the toxicity of isocyanides and amines is generally considered lower than the otherwise used reagents.[55–57] It is noted that the synthesis of isocyanides commonly entails the use of toxic reagents as well, for instance phosgene and its surrogates[58–61] or phosphorus oxychloride

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($POCl_3$),[62–65] but we recently introduced a more sustainable route using *p*-toluenesulfonic acid chloride (*p*-TsCl) obtaining non-sterically demanding aliphatic isocyanides in good yields.[66]

Results and discussion

Synthesis of thioureas via MCR

To obtain various catalytically active thioureas via the above mentioned MCR pathway, we synthesized several *N*-cyclohexyl thioureas (see Figure 1) varying the second moiety. We changed the solvents for MCRs from high-boiling DMF, and toluene, or bulk,[50,67] to methanol ($c_{isocyanide} = 1$ M), since bulk reaction conditions turned out to be troublesome in some cases due to restricted stirring Using a minimal excess of sulfur (1.12 eq. corresponding to the amount of sulfur atoms) and amine (1.10 eq.) proved to be sufficient for achieving high yields. Elevated reaction temperature (up to 80 °C) was sometimes needed to achieve full conversion or obtain higher yields. In many cases column chromatography could be avoided, and purification was performed by simple precipitation. Since Curran *et al.* had shown that the trifluoromethyl groups of an aryl moiety adjacent to the thiourea group can be partially replaced by an ester group to increase the solubility of the thiourea, while maintaining catalytic activity,[36] we decided to investigate the impact of aromatic ester moieties on the hydrogen bonding ability (compound **9**). Following this idea, a thiourea bearing an aromatic sulfone moiety (compound **10**) was prepared, expecting similar features. In addition, several other moieties (aromatic, benzylic and aliphatic) were investigated for their suitability of the new synthesis approach as well as for their hydrogen bonding activity, bearing the potential of an easier access via sustainable resources (see Figure 1).

Commercially available cyclohexyl isocyanide was first reacted with cyclohexyl-, furfuryl-, and benzyl amine, as well as with ammonia and hydrazine to obtain the corresponding thioureas **1**–**5** in one step in good yields (70–89%). Since aromatic amines are less nucleophilic, thus preventing the formation of the desired thiourea, aryl moieties were introduced via the isocyanide component, resulting in products **6**–**11** in yields between 26 and 82%. In the case of thioureas **10** and **11**, the corresponding isocyanides were found to be sensitive to moisture, as they started to decompose to the respective *N*-formamide when column chromatography was performed or remaining dehydration reagent ($POCl_3$) was quenched with aqueous sodium hydrogen carbonate solution.

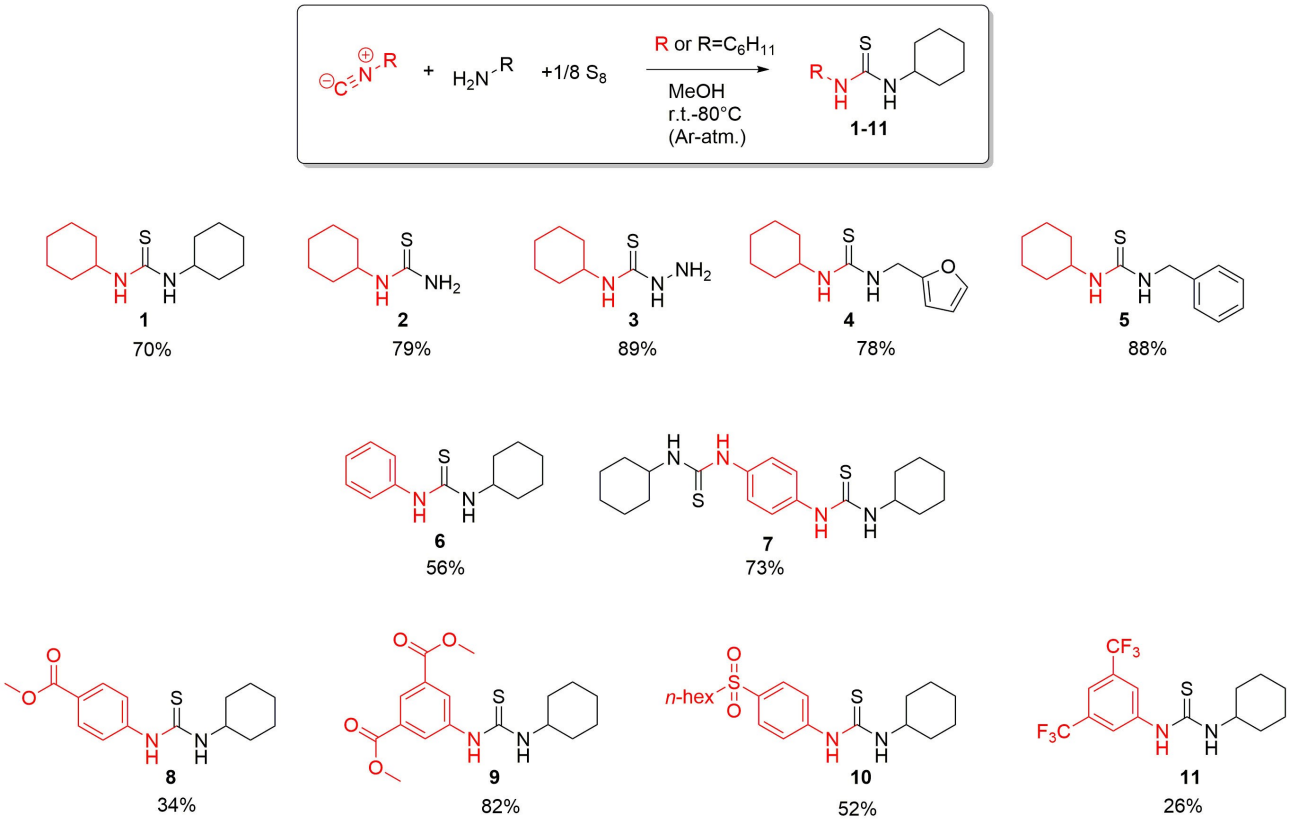


Figure 1. Overview of the synthesized N-cyclohexyl thiourea derivatives 1–11 using an MCR of an isocyanide (red moiety in the final catalyst), an amine and elemental sulfur. Cyclohexyl isocyanide and the corresponding amine component were used to prepare non-aryl thiourea derivatives, while aryl thioureas were prepared using cyclohexyl amine and the corresponding isocyanide. Since the respective isocyanide of compound 11 was sensitive to moisture, it was converted immediately after it had been formed and the given yield is referenced to the used N-formamide which was dehydrated to the isocyanide.

This observation was attributed to their higher electrophilicity resulting from the electron-withdrawing groups (EWG). In the case of the aromatic thiourea derivatives **6**–**11**, the isocyanide starting component could not be synthesized via our recently reported more sustainable synthesis protocol using *p*-TsCl as dehydration reagent,[66] as test reactions to obtain methyl 4-isocyanobenzoate (corresponding to thiourea **8**) led to very low yield (13 %).[66] Instead, the toxic $POCl_3$ had to be used in this case for the dehydration step. In summary, the synthesis of the thioureas depicted in Figure 1 is achieved in a straightforward one step reaction with acceptable to good yields, clearly demonstration the advantage of the MCR approach for the synthesis of structurally diverse organocatalysts.

Hydrogen bonding strength of thiourea compounds

In 2014, Hilt *et al.* showed that the hydrogen bond donor ability of thioureas can be quantified by ^{31}P NMR analysis of a suitable hydrogen bond acceptor (tri-*n*-butylphosphine oxide) and further correlated with their catalytic activity.[69] Formation of a thiourea phosphine oxide complex led to an downfield shift of the ^{31}P signal with increasing hydrogen bonding strength of the thiourea compound. The hydrogen bonding ability of the thioureas **1**–**11** was thus determined via ^{31}P NMR measurements following a protocol adapted from Franz *et al.*[70] using triethyl phosphine oxide ($POEt_3$) as analytical reagent (chemical shift δ in ^{31}P NMR was 51.40 ppm in $CH_2Cl_2/CDCl_3$ 4:1). Table 1 shows the chemical shift δ of the respective thiourea and the difference compared to pure $POEt_3$ (Δδ). The thioureas derived from ammonia and hydrazine (**2** and **3**) show negligible downfield shifts, as expected due to an increased electron density of the thiourea motif. Similar observations were made for **7**, bearing two thiourea groups connected by an aromatic system, but the solubility of this compound was very low and thus, these shift values should be considered with caution. Dicyclohexyl thiourea **1** showed a small downfield shift of 1.54 ppm, while benzylic moieties, as present in **4** and **5**, resulted in moderate shifts of 3.06 and 2.54 ppm, respectively, which were higher compared to the shift of phenyl thiourea **6** (2.06 ppm). While aryl ester thiourea **8** led to a moderate chemical sift of 2.86 ppm, the other electron-deficient aryl thioureas **9**–**11** exhibited higher downfield shifts, thus indicating stronger hydrogen bonding. Compared to aryl thiourea **8** bearing one ester group in *para* position, thiourea **9** showed considerably stronger hydrogen bonding due to two ester groups in *meta* position of its aromatic system, being consistent with the early findings of Schreiner that two electron-deficient substituents attached in *meta* position of the aryl thiourea group resulted in the most efficient catalyst.[2]

Applying the stronger electron-withdrawing sulfone group, hydrogen bonding was further increased based on the Δδ-value of 4.82 ppm of thiourea **10**. Even though only one sulfone group is attached to the *para*-position, sulfonaryl thiourea **10** showed stronger hydrogen bonding than both ester aryl thioureas, which was attributed to the intrinsically higher electron-withdrawing-strength of the sulfone moiety. Compound **11** was considered as a benchmark for the typically used 3,5-bis(trifluoromethyl)phenyl moieties in thiourea catalysis to determine the magnitude of chemical shift required for a thiourea compounds to be a suitable candidate as catalyst in this investigation (thiourea **11** itself was already reported as potent catalyst in aminolysis of carbonates,[71] also vide *infra*). Comparing the Δδ value of thiourea **10** and **11** (4.82 ppm and 5.14 ppm) showed that one sulfone group attached in *para* position of the aromatic moiety resulted in a slightly lower shift than two trifluoromethyl groups at each *meta* position, suggesting that compound **10** could act as a organocatalyst with a similar potential as thiourea **11**.

Table 1. Relative hydrogen bonding strength of the thioureas 1-11 determined by ^{31}P NMR measurement of a complex of $POEt_3$ and the respective thiourea. The corresponding chemical shift δ and Δ δ-values of the supramolecular complexes are listed.

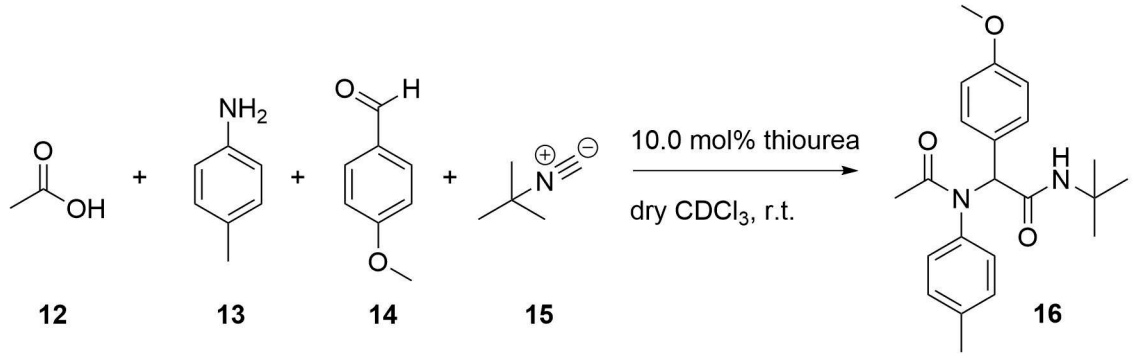
Thiourea	Chemical shift δ/ppm[a]	Δδ/ppm[a]
1[c]	52.94	1.54
2[c]	52.76	1.36
3	52.13	0.73
4	54.49	3.09
5	53.94	2.54
6[d]	53.42	2.02
7	52.44	1.05
8[b], [c]	54.26	2.86
9[c]	55.72	4.33
10	56.21	4.82
11	56.53	5.14

[a] Each thiourea compound (2.40 eq.) was added to $POEt_3$ (1.00 eq.) in a mixture of $CH_2Cl_2/CDCl_3$ (4:1). The experiments were performed three times and the average values are given. [b] The experiments were performed two times and the average is given. [c] Catalyst was not entirely soluble under the applied conditions. [d] Thiourea showed very low solubility even when the amount of solvent was doubled.

Investigations of catalytic activity in an U-4CR

Using the results of the quantification of the hydrogen bonding strength as a guide, thioureas **1**–**11** were evaluated for their catalytic activities. First, we sought to investigate the potential use of thioureas as catalysts in the U-4CR, as the mechanistic pathway of the reaction shows several steps that might profit from thiourea hydrogen bonding. For instance, thioureas are expected to increase the Brønsted acidity of the carboxylic acid component by anion stabilization and enhance the electrophilicity of the aldehyde or acylimidate by complexation (see Table 2 and Figure S1 in the Supporting Information for further details). Thus, the synthesis of **16** was followed by ^1H NMR, as conversion can easily be evaluated in this case (see Table 2). Bisamide **16** was synthesized using acetic acid **12**, *p*-toluidine **13**, *p*-methoxy benzaldehyde **14** and *tert*-butyl isocyanide **15** in dry $CDCl_3$ in the presence of 10 mol % of the respective thiourea compound. The Schreiner catalyst (bis(3,5-(trifluoromethyl)phenyl) thiourea) was tested as a reference for its catalytic activity in the U-4CR and the conversion of acetic acid was determined using the singlet signal of its CH_3 group compared to the respective signal in product **16**.

Table 2. Investigations of catalytic activity of thiourea compounds and methanol in an U-4CR leading to Ugi product 16. Conversions were determined by measuring ^{1}H NMR-spectra of the respective reactions after 66 hours, and 6 days.



12 13 14 15 16

Thiourea	Conversion after 66 h/%[a]	Conversion after 6 d/%[a]
–	14	19
1	12	17
2	14	20
3	12	16
4	14	19
5	11	17
6	16	19
7[b]	15	20
8	14	20
9	16	22
10	21	28
10[c]	n.d.	33
11	22	27
Schreiner catalyst	26	31
Schreiner catalyst[b],[c]	n.d.	33

[a] Reactions were performed with carboxylic acid (1.00 eq.), amine (1.50 eq.), isocyanide (1.50 eq.), aldehyde (1.38 eq.) and 10.0 mol% of the respective thiourea compound in dry $CDCl_3$ (concentration$_{carboxylic\ acid}$ = 0.10 M) at room temperature (r.t.). Each experiment was performed three times and the average values are given. [b] was not completely soluble. [c] 20 mol% catalyst was used.

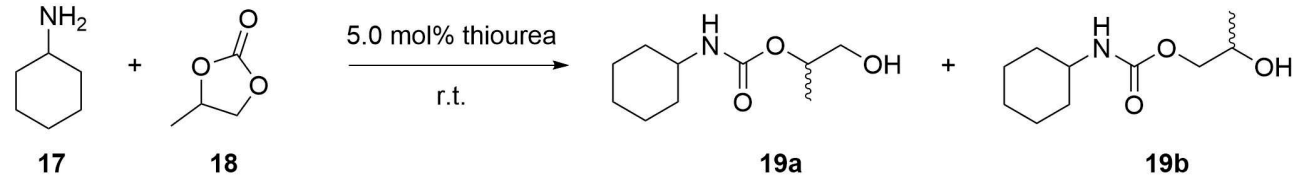
Conversions were recorded at two reaction times (66 hours, and 6 days) and are listed in Table 2. We set out to investigate the catalytic activity in rather dilute, non-optimal conditions (0.10 M corresponding to acetic acid) to enable the observation of possible catalytic effects. We note that the herein reported yields are thus lower than those obtained under commonly employed conditions (0.50 M concentration of acetic acid **12** in methanol yielded 58% of **16**).[55] Importantly, no Passerini or other side-products were detected. When thioureas **1**–**7**, all showing low to moderate hydrogen bonding according to Table 1, were used as catalysts in U-4CR, the conversion did not increase compared to the respective blind test (19% conversion, all within expected error margin). Since polar protic solvents are known to improve the conversion of Ugi-4CR reactions,[55] the addition of methanol as catalytic species (40.0 mol%) was also tested without notable effect. Aryl ester thiourea **8** did show a minimal positive effect, while aryl diester thiourea **9** led to a slightly increased conversion of 22%.

Finally, sulfonaryl thiourea **10**, showing the highest observed chemical shift in Table 1, led to an increased conversion of 28% after 6 days, which was similar to reference compound **11** (27% after 6 days). These results further confirmed the obtained data of the NMR-investigation, i.e. that compound **10** shows similar catalytic properties than compound **11**. The highest conversion of 31% after 6 days was obtained by the Schreiner catalyst, which was ascribed to its two activating moieties. Increasing the catalyst-loading to 20 mol%, catalyst **10** achieved same conversion than the Schreiner catalyst (33% conversion after 6 days). The improved performance of catalyst **10** in higher concentrations is most likely due to better solubility of this compound, since the Schreiner catalyst was not completely soluble under this condition. Although this catalytic enhancement seems small (absolute increase in yield 14%, relative increase in yield ~73%), it shows that an Ugi-4CR can be positively influences using thiourea catalysts, opening new possibilities in the field of multicomponent reactions.

Catalysis of aminolysis of propylene carbonate

In order to further explore the potential of thiourea **10** as a catalyst, we sought to use it in another reaction where its previously reported analogue, thiourea **11**, exhibited high organocatalytic activity. Therefore, the aminolysis of propylene carbonate **18** with cyclohexyl amine **17** was chosen and two carbamates **19a** and **19b** as regioisomers were obtained, as previously reported by Caillol and Andrioletti.[71] The reaction is known to be effectively catalyzed by urea and thiourea

Table 3. Aminolysis of propylene carbonate 17 with cyclohexyl amine 18 catalyzed by several thiourea compounds.



17 18 19a 19b

Catalyst	Conversion after 30 min/%[a]	Conversion after 60 min/%[a]
none	3 {5}	7 {9}
Thiourea 1	12	25
Thiourea 4	16	30
Thiourea 6	27	38
Thiourea 7[b]	21	33
Thiourea 9	55	65
Thiourea 10	59	68
Thiourea 11	64 {55}	70 {66}
Schreiner catalyst	47 {28}	58 {41}

As the viscosity of the reaction mixtures increased with conversions, we added ethyl acetate to obtain a homogeneous solution before taking a GC-sample. Values in brackets were reported in the literature. [a] Each experiment was performed three times and the average is given. Biphenyl (12.0 mol%) was used as internal standard. [b] Catalyst was not completely soluble.

compounds like thiourea **11**, among others (see Table 3). In addition, thiourea **9**, which showed minimal catalytic activity in U-4CR, as well as thiourea **1**, **6** and **7**, were tested in this aminolysis reaction.

While only 7% of conversion (9% reported in literature) was observed after one hour in the absence of any catalyst for this reaction, thiourea **11** was reported to show 66% of conversion. In our experiments, the conversion was slightly higher, obtaining 70%. Sulfonylaryl thiourea **10** yielded similar results with a conversion of 68%, confirming the similar activating effect of sulfonylaryl thiourea and aryl-CF_3 moieties already observed for the Ugi-4CR reactions. Interestingly, the conversion of the reaction using isophthalic acid ester thiourea **9** as catalyst reached 65% conversion after one hour, thus indicating that diester aryl motifs are also suitable candidates for organocatalysis. Comparing benzylic thiourea **4** with aromatic thiourea **6**, the aromatic catalyst showed a higher but still moderate activity (38% conversion after one hour). This results are contradictory to the determined hydrogen bonding strength of thiourea **4**, which was higher compared to thiourea **6** ($\Delta\delta$-value was 3.09 ppm for **4** and 2.02 ppm for **6**) underlining that hydrogen bonding strength obtained by ^{31}P NMR measurements is a good first indicator for catalytic activity of thiourea catalyst, but performance in the actual catalytic system may vary. Furthermore, dithiourea **7** showed improved performance if compared to thioureas **1** and **4**, while showing the lowest hydrogen bonding strength ($\Delta\delta$-value 1.05 ppm), which was attributed to the fact that the concentration of catalytically active thiourea functional groups was doubled due to its bis-functionality. Compared to thiourea **9**–**11**, Schreiner catalyst yielded slightly lower conversions after one hour (58%), being consistent with the results reported previously. However, the reported conversion of the Schreiner catalyst (41%) differed from our observations, most likely due to adjusted reaction conditions compared to the literature (see Table 3).

Conclusions

Various differently functionalized thiourea compounds were synthesized using a straightforward and a less hazardous synthesis protocol via an MCR of an amine, an isocyanide and elemental sulfur. The hydrogen bonding strength of the thiourea compounds was evaluated using ^{31}P NMR measurements. Subsequently, their catalytic activity was verified by applying them as catalysts in an U-4CR, revealing that sulfonylaryl thiourea moieties lead to catalysts with similar activities as catalysts bearing aryl-CF_3 groups. Subsequently, the aminolysis of propylene carbonate was evaluated, confirming that *p*-(alkylsulfonyl)phenyl and dialkylisophtalic acid ester moieties are suitable activating functional groups for thioureas in organocatalysis. Especially the sulfone group showed comparable results to the commonly used 3,5-bis (trifluoromethyl)phenyl group in all tests. The herein introduced functional groups are promising moieties for thiourea catalyst design, since they are tailorable and thus allow to increase the solubility of the respective catalyst compared to commonly applied catalysts. They furthermore broaden the scope of suitable EWGs, paving the way for a wider scope of application of thiourea compounds in organocatalysis.

Supporting Information Summary

This complementary section describes the procedure for the quantification of hydrogen bonding strength of thioureas as well as two catalysis screenings (U-4CR and aminolysis of propylene carbonate) in detail. In addition, a proposed mechanism for the activation of an U-4CR via thiourea catalysis

is depicted and discussed shortly. Furthermore, the experimental procedures and characterization of the herein reported thioureas and the preparation of their respective isocyanide precursors are given.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: hydrogen bonding · multicomponent reaction · organocatalysis · thiourea · sulfur

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