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# Chromatography-Free Multicomponent Synthesis of Thioureas Enabled by Aqueous Solution of Elemental Sulfur

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The development of a new three-component chromatography-free reaction of isocyanides, amines and elemental sulfur allowed us the straightforward synthesis of thioureas in water. Considering a large pool of organic and inorganic bases, we first optimized the preparation of aqueous polysulfide solution from elemental sulfur. Using polysulfide solution, we were able to omit the otherwise mandatory chromatography, and to isolate the crystalline products directly from the reaction mixture by a simple filtration, retaining the sulfur in the solution phase. A wide range of thioureas synthesized in this way confirmed the reasonable substrate and functional group tolerance of our protocol.

## 1. Introduction

Sulfur–containing compounds are widely used as biologically active molecules[1] and functional organic materials.[2,3] Thioureas, in particular, are important pharmaceutical and agrochemical intermediates and active ingredients represented by the marketed drug thiocarlide,[4] algicides,[5] fungicides[6] and the insecticide chloromethiuron.[7] In addition, they are key synthetic precursors of nitrogen and sulfur containing compounds, especially pharmacologically relevant heterocycles.[8–12] Notably, in the last two decades thioureas were also applied as highly selective and efficient organocatalysts.[13–16] Given the wide utility of thioureas, their clean and efficient synthesis is of high interest.

Elemental sulfur is a bench-stable environmentally benign, inexpensive and nontoxic reagent for sulfuration offering an atom-economical and safe alternative to incorporate the sulfur atom into products.[17] Certain nucleophiles, such as aliphatic amines are able to generate trisulfur radical anions[18] and open-chain ionic polysulfide anions from elemental sulfur,[19] the former existing only under inert conditions. These transformations are responsible for the activation of elemental sulfur, which can then be used as efficient sulfurating reagent.[17] Recently a couple of innovative, multicomponent and one-pot procedures have been published for the use of elemental sulfur in synthetic procedures.[20–26] Numerous methods rely on the known transformation of isocyanides to isothiocyanates with elemental sulfur in the presence of base or various metal catalysts,[19,27–35] which is utilized in particular for the synthesis of thioureas (Scheme 1). Zhou *et al.* developed a cobalt-catalyzed method for the synthesis of thioureas starting from isocyanides, elemental sulfur, aliphatic and aromatic amines under oxidative conditions.[36] The one-pot procedure of Tan *et al.* offers the *in situ* synthesis of isocyanides from amines and chloroform in the presence of potassium *tert*-butoxide, followed by the addition of sulfur and various amines.[37] It should be noted that the above mentioned methods require catalyst and organic solvents. The most practical way was introduced by Nguyen *et al.* who developed a solvent- and catalyst-free method starting from isocyanides, elemental sulfur and aliphatic amines.[38] As a limitation of this method, the preparation of biaryl thioureas is not available due to the reduced nucleophilic behavior of aromatic amines under the applied conditions. Moreover, the excess of sulfur make chromatography indispensable as crystallization from an organic solvent is not suitable for the removal of $S_8$.

Since the introduction of the 12 principles in green chemistry, considerable efforts have been made to the development of environmentally friendly and sustainable organic processes. A major aspect of green chemistry is to use safer solvents and to reduce the environmental impact of the chemical reactions.[39,40] Chromatographic purification produces large waste of organic solvents and dischargeable static phase, therefore, developing new reaction pathways and improving existing methods to avoid chromatography remains an important issue[40–46] from both environmental and economic points of view. The replacement of organic solvents with water as a non-toxic, abundant and cheap solvent has generated significant attention. Notably, its features of accelerating reactions and simplifying the isolation of the products are regarded as main advantages of its application in organic reactions.[47–50] In continuation of our interest in green chemistry,[51] multicompo-

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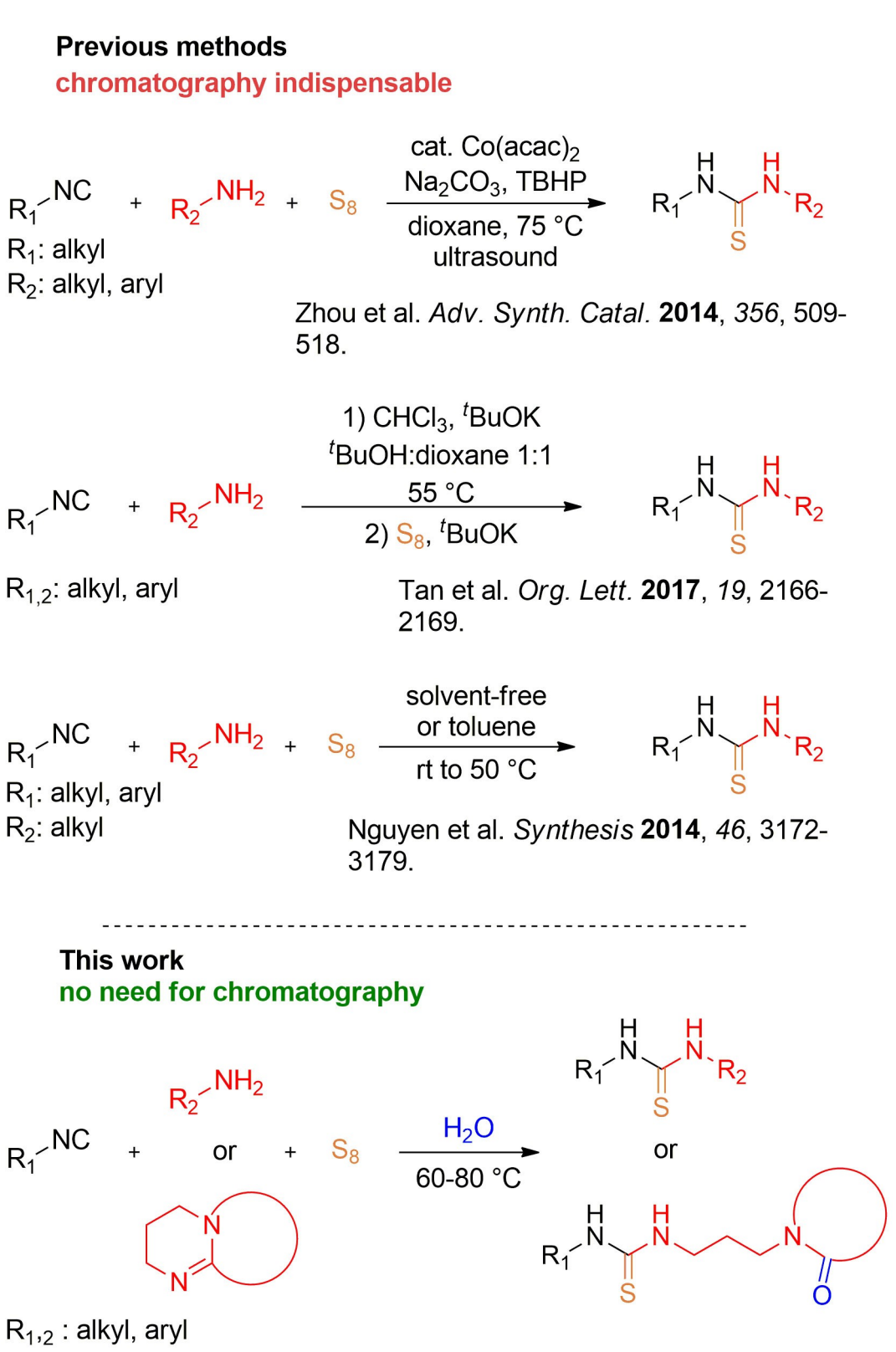


**Scheme 1.** Synthetic methods for the elemental sulfur based multicomponent synthesis of thioureas.

nent reactions[52–54] and reactions involving sulfur[19,55] we aimed to develop an environmentally friendly synthesis for diverse thioureas, including challenging biaryl derivatives. We envisioned the preparation of aqueous solutions of polysulfide anions to use it as a novel agent for the incorporation of sulfur atom. The main advantages of this reagent would be an


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environmentally friendly, atom economical access to thio compounds in water with easy work-up and purification by avoiding chromatography. As the first step in this direction, here we report the development of a chromatography-free multicomponent synthesis of thioureas in polysulfide anion containing aqueous solutions.

## 2. Results and Discussion

Our first objective was to prepare polysulfide anion containing aqueous solutions from elemental sulfur using different bases (Table 1). Optimizing the conditions, we applied 0.05 M elemental sulfur in the presence of 20 equivalents of bases including NaOH, diisopropylamine (DIPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in water. Although sonication at room temperature or at 40 °C and 60 °C failed to result in the homogeneous solution, vigorous stirring enabled the complete dissolution of the solid at 60 °C. Encouraged by the results, we have screened a number of bases in water (see ESI Table S1) and finally found 14 bases suitable for the preparation of homogenous polysulfide anion containing aqueous solutions in various concentrations (Table 1). Our goal was to reach a sulfur concentration of at least 0.1 M that is perfectly suited for synthetic purposes.[25,56–65] Generally, inorganic bases did not provide the appropriate concentration, as in the case of NaOH, $Na_2S$ and tetrabutylammonium hydroxide (TBAOH) we could reach a concentration of only 0.05 M elemental sulfur in the presence of 20 equivalents of base (entries 1–3, Table 1). Although Wang *et al.* claimed to dissolve 0.05 M sulfur and 0.34 M disodium disulfide in water at 70 °C in 15 minutes,[66] this method was not reproducible in our hands. Employing 1.0 M piperidine or 1,4-diazabicyclo[2.2.2]octane (DABCO) in water provided a 0.05 M and 0.1 M solution of sulfur, respectively (entries 4 and 11, Table 1). Considering further organic bases, such as DIPA, *N,N,N′,N′′,N′′*-pentamethyldiethylenetriamine (PMDTA) or the amidines DBU, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), we successfully prepared more concentrated, 0.4 M solutions of elemental sulfur in the presence of only 2.5 equivalents of the base (entries 5–10, Table 1). In the case of $Et_3N$, *N*-ethylpiperidine and quinine the addition of 50 % acetonitrile or tetrahydrofuran (THF) was necessary in order to keep the solution homogeneous (entries 12–14, Table 1), however, the maximal concentration was limited to 0.15 M of sulfur for 0.25 M of quinine (entry 14, Table 1). Although we achieved higher sulfur concentration in some cases, we have standardized the amount of base and elemental sulfur in 1.0 M and 0.4 M, respectively due to practical considerations (versatility, comparability and easy handling). These target concentrations were achieved by multiple bases that provided considerable flexibility for developing synthetic applications.

Polysulfide solutions were investigated by NMR in $D_2O$. Figure 1 shows the stacked $^1$H-NMR spectra obtained for the polysulfide solutions containing 0.1 M, 0.4 M and 1.0 M sulfur together with 1.0 M PMDTA in $D_2O$, respectively. Dissolving sulfur in 0.1 : 1 ratio with the base (Fig 1B), chemical shifts are shifted lower and the signals of the methyl groups 1′ and 4′ became merged at 2.08 ppm. Increasing the ratio of sulfur to 0.4 : 1 (Fig 1 C) and 1 : 1 (Fig 1D) the chemical shift of the methyl groups 1′ show a 0.13 and then a 0.14 ppm positive shift, while the methyl group 4′ is moving only 0.10 and further 0.09 ppm upwards. The signals of the ethylene groups shifts upwards as well and start to merge around 10 % sulfur content indicating that the chemical difference between the carbons 2 and 3 fades. Performing the experiments in the presence of $CF_3COOD$ instead of sulfur, we had similar observations, proving quaternization of the nitrogen atoms (see ESI Figure S1). These observations indicate that both types of nitrogen atoms are involved in the nucleophilic attack on sulfur, though the terminal nitrogen atoms participate more in the transformation. In fact, the activation energy of ammonium ion formation is very low,[67] and thus we suppose a dynamic equilibrium

**Table 1.** Suitable bases for the preparation of aqueous polysulfide solution.

| Entry[a,b] | Base | Solvent | Base/$S_8$ concentration [c] |
|---|---|---|---|
| 1 | NaOH | Water | 1.0 M/0.05 M |
| 2 | $Na_2S$ | Water | 1.0 M/0.05 M |
| 3 | TBAOH | Water | 1.0 M/0.05 M |
| 4 | Piperidine | Water | 1.0 M/0.05 M |
| 5 | DBU | Water | 1.0 M/0.4 M |
| 6 | DBN | Water | 1.0 M/0.4 M |
| 7 | TBD | Water | 1.0 M/0.4 M |
| 8 | MTBD | Water | 1.0 M/0.4 M |
| 9[d,e] | PMDTA | Water | 1.0 M/0.4 M |
| 10[e] | DIPA | Water | 1.0 M/0.4 M |
| 11[e] | DABCO | Water | 1.0 M/0.1 M |
| 12[e,f] | $Et_3N$ | Water:MeCN | 1.0 M/0.4 M |
| 13[e,f] | N-ethylpiperidine | Water:MeCN | 1.0 M/0.4 M |
| 14[e,g] | Quinine | Water:THF | 0.25 M/0.15 M |

[a] For the full list of bases, see the supporting information (Table S1). [b] Conditions: 60 °C, water, vigorous stirring. [c] Concentration of base and sulfur respectively. [d] 70 °C was employed. [e] Overnight stirring was employed. [f] 50 % acetonitrile was used as co-solvent. [g] 50 % THF was used as co-solvent.

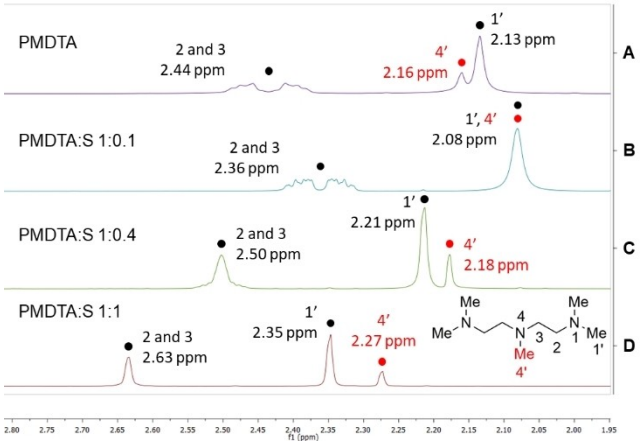


**Figure 1.** Stack plot of the 1H-NMR spectra of PMDTA and polysulfide solutions made of PMDTA and sulfur in $D_2O$ in different amine:sulfur ratios; Spectrum „A": PMDTA; Spectrum „B": PMDTA:S 1:0.1; Spectrum „C": PMDTA:S 1:0.4; Spectrum „D": PMDTA:S 1 : 1.


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between the quaternization of the terminal and the middle nitrogens.

The nucleophilicity of DBU and related amidines DBN, TBD and MTBD has been used in their reactions with aldehydes,[68] carbonates,[69] imidazolides,[70] methyl-pyrazoles[71] and benzoxazinones[72] as electrophiles leading to caprolactams or substituted tetrahydropyrimidinones. Notably, cyclic amidines undergo ring-opening in the presence of water yielding aminopropyl lactams and pyrimidinones that readily react with halobenzenes[73–75] and esters.[76] As a result of the preparation of the polysulfide solution, we observed the ring opening transformation of DBU.[73–76] Figure 2 shows the stacked spectra of DBU (Figure 2A), 1-(3-aminopropyl)azepan-2-one (Figure 2B) and the polysulfide solution prepared from 0.4 M sulfur and 1.0 M DBU (Figure 2C). Comparing these spectra and the highlighted atoms, no change in the chemical shift of the opened DBU can be observed. The protons at the position 7, 1′ and 3′ are located at the same chemical shift in the neat and polysulfide solution (Figure 2B and 2 C). The corresponding protons of DBU at the position 2, 11 and 9, respectively, however, moving upwards from 3.58, 3.54 and 3.34 ppm to 3.64, 3.59 and 3.39 ppm, respectively after the preparation of the polysulfide solution (Figure 2A and 2B). These findings suggest that the quaternization, thus the interaction of sulfur happens with DBU and the presence of 1-(3-aminopropyl) azepan-2-one is a result of the known hydrolysis of DBU (Scheme 2).[73–76] Therefore, we envisioned the reaction of the polysulfide solution of amidines (**3**) with isocyanides (**1**) in order to generate caprolactam and pyrimidinone substituted thioureas. We found this reaction suitable for the validation of the aqueous polysulfide solution to prepare isothiocyanate from isocyanide followed by the transformation to thiourea in a one-pot, multicomponent manner. Accordingly, a polysulfide solution has been made from DBU (**3 a**, 1.0 M) and sulfur (0.4 M) stirring vigorously at 60 °C for 1 hour and cooling to room temperature. Then, 0.2 mmol of 2,6-dimethylphenyl isocyanide (**1 a**, 0.2 M) was added to 1 mL polysulfide solution which provided the corresponding thiourea **4 aa** in 55 % yield at room temperature after 5 hours (Table 2, entry 1). Notably, the product precipitated from water, thus it could be separated easily by filtration. The excess of the base and polysulfide anions could be removed by washing the solid with water i.e. no chromatographic purification was necessary. Next, we optimized the conditions of this reaction isolating the products after the full consumption of the isocyanide monitored by TLC and HPLC-MS. Raising the temperature to 40 °C and 60 °C the reaction time decreased to 2 hours and 0.5 hour, resulting in **4 aa** in 74 % and 96 % yields, respectively (Table 2, entries 2, 3). Reducing the excess of sulfur to 1.5 equivalents at 60 °C

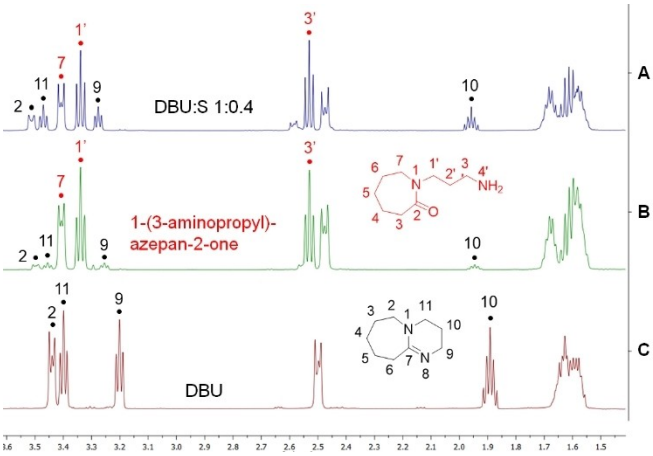
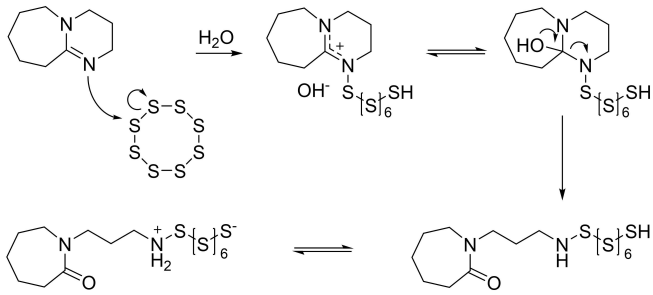
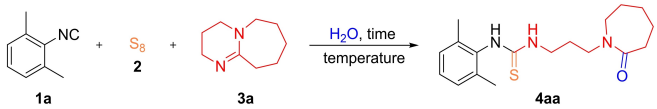



**Figure 2.** Stack plot of the $^1$H-NMR spectra of DBU (spectrum „A"), 1-(3-aminopropyl)-azepan-2-one (spectrum „B") and the polysulfide solution made of 1.0 M DBU and 0.4 M sulfur (spectrum „C") in $D_2O$.




**Scheme 2.** Proposed interaction of DBU with elemental sulfur.

**Table 2.** Optimization of the reaction conditions for the synthesis of thioureas.




| Entry | *T* [°C] | Time [h] | Molar excess of **1 a**/**2**/**3 a** | Yield[a,b] [%] |
|---|---|---|---|---|
| 1 | RT | 5 | 1/2/5 | 55 |
| 2 | 40 | 2 | 1/2/5 | 74 |
| 3 | 60 | 0.5 | 1/2/5 | 96 |
| 4[c] | 60 | 0.5 | 1/1.5/5 | 85 |
| 5[d] | 60 | 0.5 | 1/2/4 | 93 |
| 6[e] | 60 | 0.5 | 1/2/3 | 76 |
| 7[f] | 60 | 0.5 | 1/2/5 | 91 |

[a] Reaction conditions: **1 a** (0.2 mmol), polysulfide solution in water (1 mL, 1.0 M DBU (**3 a**)/0.4 M $S_8$ (**2**)), temperature, time. [b] Isolated yields. [c] Polysulfide solution in water (1 mL, 1.0 M DBU (**3 a**)/0.3 M $S_8$ (**2**)). [d] Polysulfide solution in water (1 mL, 0.8 M DBU (**3 a**)/0.4 M $S_8$ (**2**)). [e] Polysulfide solution in water (1 mL, 0.6 M DBU (**3 a**)/0.4 M $S_8$ (**2**)). [f] Performed at a 0.5 mmol scale.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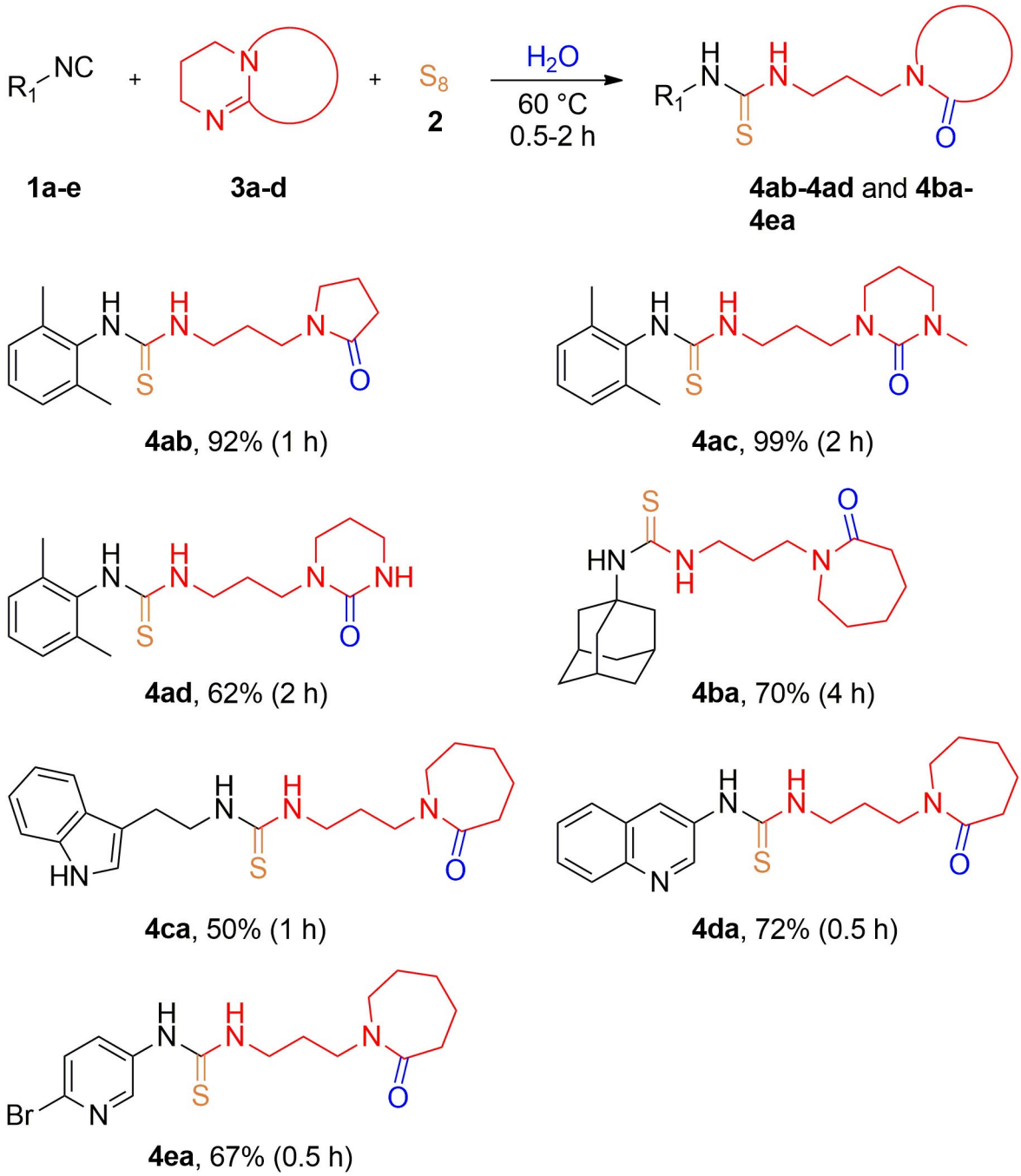
decreased the yield (85%, Table 2, entry 4). When the excess of the base was reduced to 4 equivalents (0.8 M) no significant change in the yield was observed (93%, Table 2 entry 5), however, further decreasing to 3 equivalents (0.6 M) reduced the yield significantly (76%, Table 2, entry 6). Finally, with the optimized conditions in hand (Table 2, entry 3), scaling up the reaction to 0.5 mmol provided **4aa** in 91% yield (Table 2, entry 7).

The optimized conditions scaled to 0.5 mmol (Table 2, entry 7) were applied to a structurally diverse set of amidines (**3a–d**) and isocyanides (**1a–e**) to investigate the scope and limitation of the method developed. Using 2,6-dimethylphenyl isocyanide (**1a**) with the polysulfide containing aqueous solutions made of DBN (**3b**) and MTBD (**3c**) at 60 °C provided thioureas **4ab** and **4ac** in excellent, 92% and 99% yields, respectively (Scheme 3). Applying TBD (**3d**) as base, the desired thiourea (**4ad**) was obtained in 62% yield after 2 hours. The adamantyl derivative **4ba** was isolated in 70% yield after 4 hours. Next, we applied heterocyclic thioureas containing indole, quinoline or pyridine ring **4ca–4ea** in 72%, 50% and




**Scheme 3.** Substrate scope for amidines and isocyanides. [a] Reaction conditions: **1** (0.5 mmol), polysulfide solution (1.0 M base (**3**)/0.4 M $S_8$ (**2**), 2.5 mL), reaction time in parentheses, 60 °C, water.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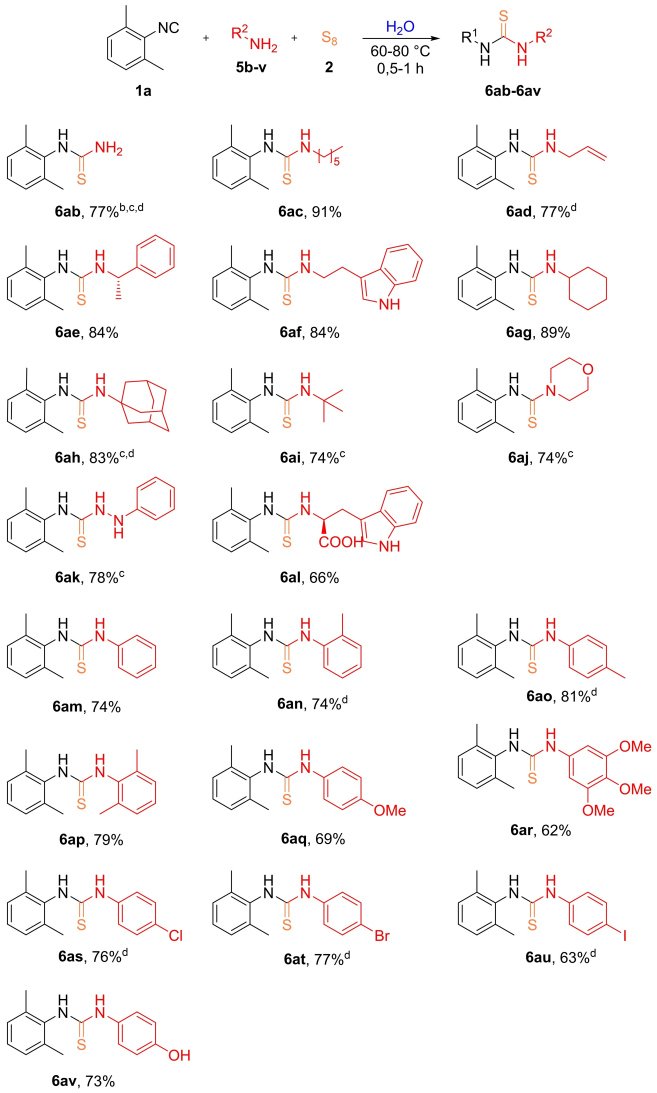
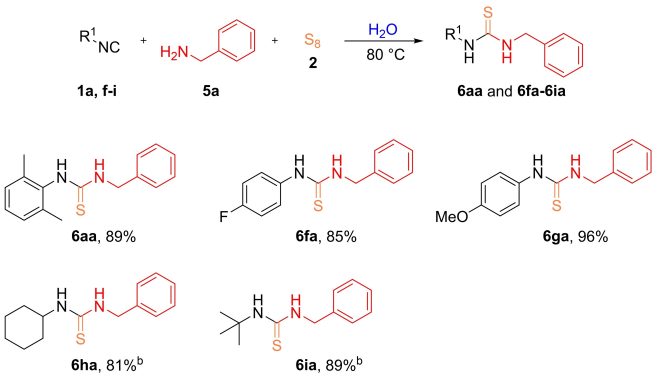
67% yields, respectively (Scheme 3). Notably, the aromatic bromine on the pyridine ring (**1e**) was well tolerated.

Considering bases resistant to acylating agents such as DABCO, PMDTA, $Et_3N$, *N*-ethylpiperidine and quinine (Table 1), the reaction was envisaged to provide virtually any desired thioureas. Since DABCO enables the preparation of only 0.1 M solution of sulfur and the latter three bases require co solvents, the generality of the reaction was investigated using PMDTA (1.0 M) and sulfur (0.4 M, Table 1, entry 9) with various isocyanides and benzylamine at 80 °C (**5a**, Scheme 4). Applying aromatic 2,6-dimethylphenyl- (**1a**), 4-fluorophenyl- (**1f**) and 4-methoxyphenyl isocyanide (**1g**), the formation of thioureas **6aa**, **6fa** and **6ga** was observed in excellent yields (89%, 85% and 96%, respectively on Scheme 4). The cyclohexyl and *tert*-butyl derivatives **6ha** and **6ia** were obtained in slightly lower but still reasonable yields of 81% and 89%, respectively. Importantly, the formed thioureas crushed out of water and were separated by filtration, no further purification was necessary.

Next, we evaluated the scope of aliphatic and aromatic amines. Aqueous ammonia (**5b**), and primary amines, like hexylamine, allylamine, (*S*)-(-)-1-phenylethylamine, tryptamine and cyclohexylamine (**5c-g**) reacted well leading to the formation of the corresponding thioureas (**6ab**–**6ag**) in good to excellent yields (77–91%, Scheme 5), in the case of **6ab** and **6ad** at 80 °C. Sterically more challenging *tert*-butylamine (**6ai**) and morpholine (**6aj**) derivatives were both isolated in 74% yield after 0.5 h at 80 °C, applying 3 equivalents of amine. 1-Adamantylamine (**5h**) was used in 3 equivalents for 1 hour at 80 °C, providing the desired thiourea **6ah** in 83% yield. Employing phenylhydrazine (**5k**) and *L*-tryptophan (**5l**) in the reaction led to the formation of the thiosemicarbazide **6ak** and thiourea **6al** in good yields (78% and 66%, respectively), the latter being isolated in a two-step crystallization procedure (see experimental section). Next, we have aimed to investigate the synthesis of biaryl thioureas. As we mentioned in the introduction, the preparation of biaryl derivatives has been only accomplished in the presence of a catalyst or in organic solvents under inert conditions.[36,37] The practical, catalyst- and solvent-free method of Nguyen et al., however, is not suitable for the synthesis of these compounds.[38] Using the polysulfide solution made of PMDTA (1.0 M) and sulfur (0.4 M, Table 1, entry 9) in the presence of 3 equivalents of aniline (**5m**) and 2,6-dimethylphenyl isocyanide (**1a**) at 80 °C eventually led to full conversion of the isocyanide in 0.5 hour. After removing the excess of polysulfide anions and the base with water, the excess of the aniline was washed away with 1.0 M aq. HCl providing the thiourea **6am** in 74% yield. The 2-methyl (**5n**) and 4-methyl (**5o**) derivatives reacted in 1 hour providing the corresponding thioureas **6an** and **6ao** in 74% and 81% yields, respectively. However, the 2,6-dimethyl- (**5p**), 4-methoxy- (**5q**), 3,4,5-trimethoxy- (**5r**) and 4-hydroxy aniline (**5v**) reacted faster, giving the thioureas **6ap**–**6aq** and **6av** in only 0.5 hour in good yields (79%, 69%, 62% and 73% respectively, Scheme 5). Halogens (Cl, Br, I) were generally well




**Scheme 5.** Substrate scope for amines. [a] Reaction conditions: **1** (0.50 mmol), **5** (0.75 mmol), polysulfide solution (1.0 M PMDTA/0.4 M $S_8$ (**2**), 2.5 mL), 60 °C, 0.5 hour, water. [b] 10 equivalents of aq. 25% $NH_3$. [c] 80 °C and 3 equivalents of **5**. [d] 1 hour reaction time. [e] In the case of anilines, 3 equivalents of **5**, 80 °C.




**Scheme 4.** Substrate scope for isocyanides. [a] Reaction conditions: **1** (0.50 mmol), **5a** (0.75 mmol), polysulfide solution (1.0 M PMDTA/0.4 M $S_8$ (**2**), 2.5 mL), 80 °C, 0.5 hour, water. [b] 2 hours reaction time.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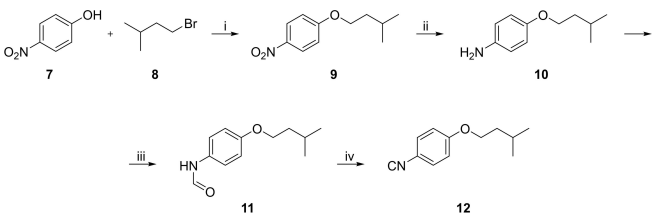
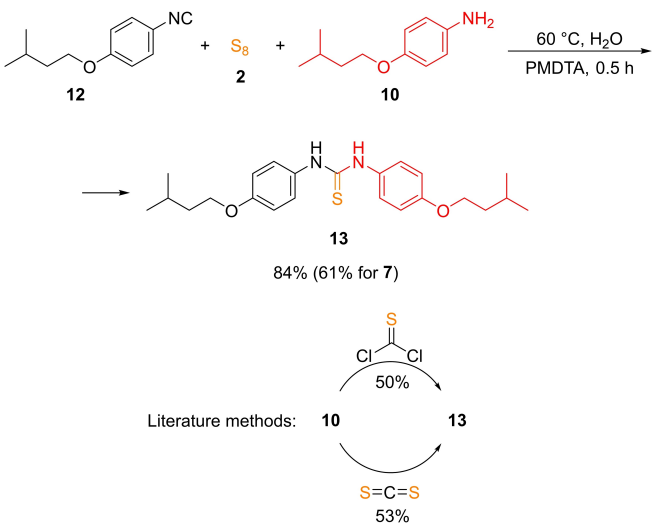
tolerated in the reaction, the thioureas **6as–6au** were obtained in 76%, 77% and 63% yields, respectively. Hence, this simple approach was used efficiently for the preparation of challenging biaryl thioureas starting from 2,6-dimethyl isocyanide, aqueous polysulfide solution and the corresponding anilines.

Next, as an eye-catching example, we have synthesized the marketed drug thiocarlide (Isoxyl®).[4] At first, 1-(isopentyloxy)-4-nitrobenzene (**9**) was prepared from the commercially available 4-nitrophenol **7** with isopentyl-bromide (**8**) in refluxing DMF in the presence of NaOH in 70% yield (Scheme 6). Then, the reduction of the nitro group by catalytic hydrogenation and the subsequent transformation of amine **10** provided the formamide **11** in quantitative yield. The formal dehydration of **11** led to the corresponding isocyanide **12** in 73% yield. In the reaction of isocyanide **12**, amine **10** and the aqueous polysulfide solution made of PMDTA (1.0 M) and sulfur (0.4 M, Table 1, entry 9) led to thiocarlide (**13**) in full conversion after 0.5 hour at 60 °C (Scheme 7). Compound **13** precipitated from water, enabling the separation by filtration. The excess of the polysulfide anions, the base and the amine was removed by washing with water and with 0.5 M aq. HCl resulting in an isolated yield of 84%. In conclusion, our method (Scheme 9) have provided better overall yield (61% for 4 steps) for the synthesis of thiocarlide starting from 4-(isopentyloxy)aniline (**10**) than that of published procedures using carbon disulfide[77] (53%) or thiophosgene[78] (50%).




**Scheme 6.** Synthesis of the key intermediates **10** and **12** for the preparation of thiocarlide. [a] Reaction conditions: (i): NaOH, DMF, reflux, 3 hours; (ii): $H_2$, 10% Pd/C, EtOAc, rt; (iii): HCOOH, $(CH_3CO)_2O$, THF, RT; (iv): $POCl_3$, $Et_3N$, THF, RT.




**Scheme 7.** Synthesis of thiocarlide in the three component reaction applying polysulfide solution in water and known literature methods.

## 3. Conclusions

In summary, we have prepared aqueous solutions of polysulfide anions from elemental sulfur with a pool of organic and inorganic bases. The resulting aqueous solutions were used efficiently for the chromatography-free synthesis of thioureas in a multicomponent reaction in good to excellent yields. This approach enables the easy isolation of the desired products by a simple filtration, and thus, introduces an environmentally benign synthesis of thioureas. The methodology has been validated in a wide range of synthesis scenarios including lactam-, tetrahidropyrimidin-2-one and other, disubstituted thioureas, highlighting biaryl derivatives and the marketed drug, thiocarlide.

## Experimental Section

### General

All melting points were determined on a Jasco SRS OptiMelt apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ or $CDCl_3$ solution at room temperature, on a Varian Unity Inova 500 spectrometer (500 and 125 MHz for $^1$H and APT NMR spectra, respectively), with the residual solvent signal as the lock and TMS as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. HPLC–MS measurements were performed using a Shimadzu LCMS-2020 device equipped with a Reprospher 100 C18 (5 µm; 100×3 mm) column and positive-negative double ion source (DUIS±) with a quadrupole MS analyzer in a range of 50–1000 m/z. The samples were eluted with gradient elution using eluent A (0.1% formic acid in water) and eluent B (0.1% formic acid in acetonitrile). Flow rate was set to 1.5 mL/min. The initial condition was 5% B eluent, followed by a linear gradient to 100% B eluent by 1.5 min, from 1.5 to 4.0 min 100% B eluent was retained; and from 4.0 to 4.5 min back to initial condition with 5% B eluent and retained to 5 min. The column temperature was kept at room temperature, and the injection volume was 1–10 µL. The purity of the compounds was assessed by HPLC with UV detection at 215 and 254 nm; all starting compounds are known, purchased or synthetically feasible and >95% pure.

### General Procedure for the Preparation of Aqueous Solutions of Polysulfide Anions

Sulfur (32 mg, 1.0 mmol) was added to a mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (373 µL, 2.5 mmol) and water (2.13 mL) and stirred vigorously at 60 °C until the complete dissolution of sulfur.

### 3.1. General Procedure for the Synthesis of Thioureas

Isocyanide (**1a–i**, 0.5 mmol) was added to the aqueous solution of sulfur and the appropriate base (**3a–d** or PMDTA, 2.5 mL, 1.0 M base, 0.4 M sulfur) and stirred vigorously at 60 or 80 °C until the total consumption of the isocyanide monitored by HPLC-MS


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**Table 3.** Preparation of polysulfide solutions according to the general procedure.

| Amine | Sulfur [mg, mmol] | Amine [µL or mg, mmol] | Water [mL] | *T* [°C] |
|---|---|---|---|---|
| 1,5-Diazabicyclo[4.3.0]non-5-ene | 32, 1.00 | 310, 2.50 | 2.19 | 60 |
| 1,5,7-Triazabicyclo[4.4.0]dec-5-ene | 32, 1.00 | 348, 2.50 | 2.50 | 60 |
| 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene | 32, 1.00 | 360, 2.50 | 2.17 | 60 |
| *N,N,N′,N′,N″*-pentamethyldiethylenetriamine | 32, 1.00 | 522, 2.50 | 1.98 | 70 |
| 1,4-Diazabicyclo[2.2.2]octane | 8, 0.25 | 280, 2.50 | 2.50 | 60 |
| Triethylamine | 32, 1.00 | 348, 2.50 | 2.16[a] | 60 |
| *N*-ethylpiperidine | 16, 0.50 | 343, 2.50 | 2.16[a] | 60 |
| Quinine | 12, 0.38 | 203, 0.63 | 2.50[b] | 60 |

[a] 1:1 mixture of water and acetonitrile. [b] 1:1 mixture of water and THF.

(between 0.5 and 4 hours). Afterwards, the product was filtered and washed with water and in the case of poorly water soluble amines with 0.5 or 1.0 M aq. HCl, then water providing thioureas **4** and **6** in 50–99% yield.

**1-(2,6-Dimethylphenyl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (4aa)**: White solid, m.p. 163–164 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.25 (bs, 1H), 7.21–7.14 (m, 3H), 6.38 (bs, 1H), 3.57 (t, 2H, *J*=6.0 Hz), 3.29–3.27 (m, 4H), 2.41−2.38 (m, 2H), 2.27 (s, 6H), 1.77−1.60 (m, 8H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 176.3 (C), 137.2 (C), 128.8 (CH), 110.0 (C), 49.8 ($CH_2$), 45.2 ($CH_2$), 41.9 ($CH_2$), 37.1 ($CH_2$), 29.9 ($CH_2$), 28.6 ($CH_2$), 27.5 ($CH_2$), 23.4 ($CH_2$), 18.1 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{28}N_3O_S$ 334.1947; found 334.1960.

**1-(2,6-Dimethylphenyl)-3-(3-(2-oxopyrrolidin-1-yl)propyl)thiourea (4ab)**: White solid, m.p. 154–155 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.27 (bs, 1H), 7.22−7.14 (m, 3H), 6.32 (bs, 1H), 3.54 (bs, 2H), 3.36 (t, 2H, *J*=7.0 Hz), 3.18 (bs, 2H), 2.32−2.24 (m, 2H), 2.27 (s, 6H), 2.01−1.95 (m, 2H), 1.79−1.76 (m, 2H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 175.6 (C), 137.3 (C), 128.8 (CH), 47.3 ($CH_2$), 41.7 ($CH_2$), 39.5 ($CH_2$), 30.8 ($CH_2$), 26.7 ($CH_2$), 18.1 ($CH_3$), 17.9 ($CH_2$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{24}N_3OS$ 306.1634; found 306.1651.

**1-(2,6-Dimethylphenyl)-3-(3-(3-methyl-2-oxotetrahydropyrimidin-1(2H)-yl)propyl)thiourea (4ac)**: Yellow crystals, m.p. 156–157 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 8.67 (bs, 1H), 7.05 (m, 3H), 6.11 (bs, 1H), 3.77−3.74 (m, 2H), 3.26−3.20 (m, 7H), 3.10−3.08 (m, 2H), 2.13 (s, 6H), 1.82−1.77 (m, 4H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.8 (C), 155.8 (C), 139.1 (C), 136.9 (C), 127.9 (CH), 126.8 (CH), 45.3 ($CH_2$), 44.5 ($CH_2$), 25.7 ($CH_2$), 22.6 ($CH_2$), 18.5 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{28}N_4OS$ 335.1900; found 335.1920.

**1-(2,6-Dimethylphenyl)-3-(3-(2-oxotetrahydropyrimidin-1(2*H*)-yl) propyl)thiourea (4ad)**: White solid, m.p. 142–143 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.27 (bs, 1H), 7.18−7.11 (m, 3H), 6.67 (bs, 1H), 4.50 (bs, 1H), 3.59−3.56 (m, 2H), 3.20−3.18 (m, 6H), 2.25 (s, 6H), 1.88−1.86 (m, 2H), 1.76−1.71 (m, 2H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 156.6 (C), 150.7 (C), 144.6 (C), 137.3 (C), 128.7 (CH), 45.3 ($CH_2$), 44.3 ($CH_2$), 41.9 ($CH_2$), 40.3 ($CH_2$), 27.0 ($CH_2$), 22.1 ($CH_2$), 18.1 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{25}N_4OS$ 321.1743; found 321.1759.

**1-((3s,5s,7s)-Adamantan-1-yl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (4ba)**: Yellow gum; $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.22 (bs, 1H), 5.90 (bs, 1H), 3.61−3.57 (m, 2H), 3.37 (t, *J*=5.8 Hz, 2H), 3.32 (t, *J*=4.7 Hz, 2H), 2.51 (t, *J*=5.7 Hz, 2H), 2.09 (bs, 3 H), 2.02 (bs, 6H), 1.73−1.62 (m, 14H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 179.7, 177.0, 53.8, 49.9, 45.6, 41.9, 41.6, 37.2, 35.9, 30.0, 29.5, 28.7, 27.2, 23.5 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{34}N_3OS$ 364.2417; found 364.2408.

**1-(2-(1H-Indol-3-yl)ethyl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (4ca)**: Yellow gum; $^1$H-NMR: (500 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.56 (d, *J*=7.9 Hz, 1H), 7.33 (d, *J*=8.1 Hz, 1H), 7.15 (t, *J*=7.2 Hz, 1H), 7.08 (t, *J*=7.8 Hz, 1H), 6.97 (d, *J*=1.6 Hz, 1H), 6.13 (bs, 1H), 3.68 (bs, 2H), 3.51 (bs, 2H), 3.34−3.26 (m, 4H), 3.00 (t, *J*=6.6 Hz, 2H), 2.48 (t, *J*=5.5 Hz, 2H), 1.70−1.59 (m, 8H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 177.3, 136.5, 132.6, 132.1, 127.2, 122.6, 122.1, 119.4, 118.6, 111.3, 49.7, 45.2, 41.0, 37.1, 29.9, 28.3, 26.6, 24.7, 23.4 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{29}N_4OS$ 373.2056; found 373.2074.

**1-(3-(2-Oxoazepan-1-yl)propyl)-3-(quinolin-3-yl)thiourea (4da)**: Beige crystals, m.p. 134–135 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 9.18 (bs, 1H), 8.82 (s, 1H), 8.37 (s, 1H), 7.96 (d, *J*=8.4 Hz, 1H), 7.85 (bs, 1H), 7.71 (d, *J*=8.1 Hz, 1H), 7.55 (t, *J*=7.9 Hz, 1H), 7.43 (d, *J*=7.7 Hz, 1H), 3.62 (d, *J*=5.4 Hz, 2H), 3.36 (t, *J*=6.1 Hz, 2H), 3.26 (t, *J*=4.5 Hz, 2H), 2.39 (t, *J*=5.4 Hz, 2H), 1.77 (m, 2H), 1.64 (d, *J*=5.2 Hz, 2H), 1.55 (d, *J*=4.4 Hz, 4H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 181.0 (C), 177.1 (C), 147.6 (CH), 145.7 (C), 131.7 (C), 129.0 (CH), 128.8 (CH), 128.2 (bs, CH), 128.0 (C), 127.8 (CH), 127.1 (CH), 49.8 ($CH_2$), 45.6 ($CH_2$), 41.6 ($CH_2$), 37.1 ($CH_2$), 29.8 ($CH_2$), 28.4 ($CH_2$), 26.8 ($CH_2$), 23.3 ($CH_2$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{25}N_4OS$ 357.1743; found 357.1736.

**1-(6-Bromopyridin-3-yl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (4ea)**: White solid, m.p. 182–183 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.77 (bs, 1H), 8.40 (d, *J*=2.7 Hz, 1H), 8.01 (bs, 1H), 7.94 (d, *J*=6.9 Hz, 1H), 7.56 (d, *J*=8.6 Hz, 1H), 3.36−3.30 (m, 6H), 2.42 (t, *J*=5.6 Hz, 2H), 1.72−1.54 (m, 8H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 181.2 (C), 175.3 (C), 145.1 (CH), 136.9 (C), 135.2 (C), 134.1 (CH), 127.7 (CH), 49.0 ($CH_2$), 45.4 ($CH_2$), 42.0 ($CH_2$), 37.0 ($CH_2$), 29.7 ($CH_2$), 28.8 ($CH_2$), 27.5 ($CH_2$), 23.5 ($CH_2$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{22}BrN_4OS$ 385.0692; found 385.0699.

**1-Benzyl-3-(2,6-dimethylphenyl)thiourea (6aa)**: White solid 106–107 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.33−7.26 (m, 5H), 7.20−7.12 (m, 3H), 5.64 (bs, 1H), 4.87 (d, *J*=5.3 Hz, 2H), 2.28 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 181.4 (C), 137.7 (C, bs), 137.3 (C), 129.0 (CH), 128.7 (CH), 127.6 (CH), 127.5 (CH), 49.2 ($CH_2$), 18.1 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{19}N_2S$ 271.1263; found 271.1261.

**1-Benzyl-3-(4-fluorophenyl)thiourea (6fa)**: Brown solid, m.p. 112–113 °C (water; ref.[79] 106−108 °C); $^1$H-NMR: (500 MHz, DMSO-$d_6$, ref.[79]) δ 9.54 (bs, 1H), 8.13 (bs, 1H), 7.44−7.41 (m, 2H), 7.34−7.33 (m, 4H), 7.27−7.24 (m, 1H), 7.16 (t, *J*=8.8 Hz, 2H), 4.73 (d, *J*=5.4 Hz, 2H) ppm.

**1-Benzyl-3-(4-methoxyphenyl)thiourea (6ga)**: Brown solid, m.p. 90–91 °C (water; ref.[80] 113–114 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[80]) δ 7.82 (bs, 1H), 7.34−7.27 (m, 5H), 7.16 (d, *J*=8.6 Hz, 2H), 6.91 (d,


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$J=8.6$ Hz, 2H), 6.09 (bs, 1H), 4.87 (d, $J=5.2$ Hz, 2H), 3.80 (s, 3H) ppm.

**1-Benzyl-3-cyclohexylthiourea (6ha)**: Beige solid, m.p. 108–109 °C (water; ref.[81] 89–90 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[82]) δ 7.34−7.30 (m, 5H), 6.16 (bs, 1H), 5.79 (bs, 1H), 4.62 (bs, 2H), 3.85 (bs, 1H), 1.95−1.93 (m, 2H), 1.65−1.56 (m, 3H), 1.34−1.13 (m, 5H) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{21}N_2S$ 249.1419; found 249.1419.

1-Benzyl-3-(*tert*-butyl)thiourea (6ia): White solid, m.p. 93–94 °C (water; ref.[83] 94 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, mixture of E/Z isomers, ref[83]) δ 7.38−7.30 (m, 5H), 6.01 (bs, 1H), 5.86 (bs, 1H), 4.78−4.77 (m, 2H), 1.39 (s, 9H) ppm.

**1-(2,6-Dimethylphenyl)thiourea (6ab)**: White solid, m.p. 184–185 °C (water; ref.[84] 205–207 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, mixture of E/Z isomers ref.[85]) δ 7.77 (bs, 1H), 7.22−7.19 (m, 1H), 7.15−7.13 (m, 2H), 6.23 (bs, 1H), 5.33 (bs, 1H), 2.30 (s, 6H) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_9H_{13}N_2S$ 181.0793; found 181.0799.

**1-(2,6-Dimethylphenyl)-3-hexylthiourea (6ac)**: White solid, m.p. 92–93 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.39 (bs, 1H), 7.21−7.18 (m, 1H), 7.14−7.13 (m, 2H), 5.32 (bs, 1H), 3.57 (q, $J=6.7$ Hz, 2H), 2.26 (s, 6H), 1.49−1.46 (m, 2H), 1.23 (m, 6H), 0.84 (t, $J=6.9$ Hz, 2H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 180.9 (C), 137.4 (C), 129.0 (CH), 128.9 (CH), 45.3 ($CH_2$), 31.3 ($CH_2$), 29.2 ($CH_2$), 26.4 ($CH_2$), 22.5 ($CH_2$), 18.0 ($CH_3$), 13.9 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{25}N_2S$ 265.1732; found 265.1736.

**1-Allyl-3-(2,6-dimethylphenyl)thiourea (6ad)**: Beige solid, m.p. 64–65 °C (water; ref.[86] 75 °C); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.18−7.12 (m, 3H), 5.83−5.78 (m, 1H), 5.38 (bs, 1H), 5.08−5.06 (m, 2H), 4.23 (m, 2H), 2.26 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 181.1 (C), 137.3 (C), 133.6 (CH), 129.0 (bs, CH), 116.7 ($CH_2$), 47.5 ($CH_2$), 18.1 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{17}N_2S$ 221.1106; found 221.1114.

**(*S*)-1-(2,6-Dimethylphenyl)-3-(1-phenylethyl)thiourea (6ae)**: White solid, m.p. 117–118 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$, mixture of E/Z isomers) δ 7.56 (bs, 1H), 7.30−7.11 (m, 8H), 5.75 (bs, 1H), 5.48 (bs, 1H), 2.24 ((two signals: 2.30 (s), 2.17 (s)) 6H), 1.48 ((two signals: 1.48 (s), 1.47 (s)) 3H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 180.3, 142.4, 137.3, 132.7, 129.0 (bs), 128.6 (bs), 127.4 (bs), 126.0, 53.8, 21.2 (bs), 18.0 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{21}N_2S$ 285.1419; found 285.1426.

**1-(2-(1H-indol-3-yl)ethyl)-3-(2,6-dimethylphenyl)thiourea (6af)**: Beige solid, m.p. 174–175 °C (water; ref.[87] 184–186 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, ref[87]) δ 7.93 (bs, 1H), 7.53 (d, $J=7.9$ Hz, 1H), 7.33 (d, $J=8.1$ Hz, 1H), 7.22−7.11 (m, 3H), 7.07 (d, $J=7.5$ Hz, 1H), 7.02 (d, $J=7.5$ Hz, 2H), 6.78 (s, 1H), 5.41 (bs, 1H), 3.91 (q, $J=6.4$ Hz, 2H), 2.99 (q, $J=6.8$ Hz, 2H), 2.08 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 137.4, 136.6, 132.8, 129.1, 127.2, 122.5, 122.1, 119.8, 118.8, 112.5, 111.3, 45.4, 25.0, 18.0 ppm.

**1-Cyclohexyl-3-(2,6-dimethylphenyl)thiourea (6ag)**: White solid, m.p. 124–125 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 7.20−7.12 (m, 3H), 5.14 (bs, 1H), 4.24 (bs, 1H), 2.25 (s, 6H), 1.99−1.97 (m, 2H), 1.60−1.58 (m, 3H), 1.39−1.34 (m, 2H), 1.07−0.97 (m, 3H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 179.5, 137.3, 129.0 (bs), 128.9 (bs), 110.0, 53.6, 32.8, 25.4, 24.7, 18.0 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{23}N_2S$ 263.1576; found 263.1579.

**1-((1*S*,3*R*,5*S*)-Adamantan-1-yl)-3-(2,6-dimethylphenyl)thiourea (6ah)**: White solid, m.p. 145–146 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.19−7.11 (m, 3H), 7.03 (bs, 1H), 5.16 (bs, 1H), 2.26 (s, 6H), 2.12 (s, 6H), 2.06 (s, 3H), 1.64 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 137.2, 128.9 (bs), 128.8 (bs), 110.0, 54.1, 41.6 (bs), 36.2, 29.5, 18.1 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{27}N_2S$ 315.1889; found 315.1889.

**1-(*tert*-Butyl)-3-(2,6-dimethylphenyl)thiourea (6ai)**: White solid, m.p. 123–124 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 7.19−7.11 (m, 4H), 5.27 (bs, 1H), 2.25 (s, 6H), 1.43 (s, 9H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 137.1, 128.9 (bs), 128.8 (bs), 110.0, 53.6, 28.9 (bs), 18.1 (bs) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{13}H_{21}N_2S$ 237.1419; found 237.1419.

***N*-(2,6-Dimethylphenyl)morpholine-4-carbothioamide (6aj)**: White solid, m.p. 163–164 °C (water; ref.[88] 138–140 °C); $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[88]) δ 7.15−7.08 (m, 3H), 6.84 (bs, 1H), 3.84 (t, $J=4.4$ Hz, 2H), 3.73 (t, $J=5.1$ Hz, 2H), 2.25 (s, 6H) ppm.

***N*-(2,6-Dimethylphenyl)-2-phenylhydrazine-1-carbothioamide (6ak)**: White solid, m.p. 194–195 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$, mixture of E/Z isomers) δ 9.53 (bs, 1H), 9.40 (bs, 1H), 8.07 (bs, 1H), 7.23 (t, $J=7.1$ Hz, 2H), 7.07−7.03 (m, 3H), 6.82 (m, 3H), 2.19 ((two signals: 2.23 (s), 2.14 (s)), 6H), ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 136.8, 129.2, 127.9 (bs), 127.0 (bs), 120.0 (bs), 113.4, 18.5 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{18}N_3S$ 272.1215; found 272.1221.

**((2,6-Dimethylphenyl)carbamothioyl)-*L*-tryptophan (6al)**: After complete consumption of the isocyanide, the reaction mixture was acidified with 10% aq. HCl and the precipitate was filtered. Next, the crude product was treated with 1.0 M aq. NaOH at room temperature for 0.5 h and the mixture was filtered. Then, the product was precipitated with 10% aq. HCl and filtered to provide the thiourea **6al** in 66% yield. Yellow solid, m.p. 120–121 °C (water); $^1$H-NMR: (500 MHz, $CDCl_3$, mixture of E/Z isomers) δ 8.06 (s, 1H), 7.82 (s, 1H), 7.36 (d, $J=7.5$ Hz, 1H), 7.28 (d, $J=8.2$ Hz, 1H), 7.14 (t, $J=7.4$ Hz, 1H), 7.06 (t, $J=7.6$ Hz, 1H), 7.00 (t, $J=7.5$ Hz, 1H), 6.93−6.89 (m, 2H), 6.72 (s, 1H), 5.63 (d, $J=6.2$ Hz, 1H), 5.35 (d, $J=5.8$ Hz, 1H), 3.35 (dd, $J_1=14.7$ Hz, $J_2=4.8$ Hz, 1H), 3.21 (dd, $J_1=14.9$ Hz, $J_2=6.4$ Hz, 1H), 2.06 (s, 3H), 1.84 (s, 3H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 180.7 (C), 176.0 (C), 137.2 (C), 137.0 (C), 136.0 (C), 132.1 (C), 128.9 (CH), 128.7 (CH), 127.3 (C), 122.8 (CH), 122.2 (CH), 120.0 (CH), 118.1 (CH), 111.2 (CH), 109.1 (C), 57.8 (CH), 27.0 ($CH_2$), 17.7 ($CH_3$), 17.6 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{22}N_3O_2S$ 368.1427; found 368.1430.

**1-(2,6-Dimethylphenyl)-3-phenylthiourea (6am)**: White solid, m.p. 170–171 °C (water; ref.[89] 203–205 °C); $^1$H-NMR: (500 MHz, DMSO-$d_6$, ref.[90]) δ 9.87 (bs, 1H), 8.98 (bs, 1H), 7.52−7.09 (m, 8H), 2.22 (s, 6H) ppm.

**1-(2,6-Dimethylphenyl)-3-(*o*–tolyl)thiourea (6an)**: White solid, m.p. 205–206 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.40 (bs, 1H), 8.63 (bs, 1H), 7.28−7.05 (m, 7H), 2.29−2.19 (m, 9H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 137.2 (bs), 136.6. (bs), 136.4 (bs), 130.5 (bs), 128.3 (bs), 128.1, 127.7, 127.5 (bs), 126.4 (bs), 120.0, 18.0, 17.7 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{19}N_2S$ 271.1263; found 271.1272.

**1-(2,6-Dimethylphenyl)-3-(*p*–tolyl)thiourea (6ao)**: White solid, m.p. 156–157 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.75 (bs, 1H), 8.84 (bs, 1H), 7.34−7.08 (m, 7H), 2.28 (s, 3H), 2.21 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.2, 137.2 (bs), 136.8, 136.3, 133.7, 129.2 (bs), 128.8, 128.1, 127.6 (bs), 126.7 (bs), 123.9, 123.6 (bs), 20.5, 18.1 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{19}N_2S$ 271.1263; found 217.1268.

**1,3-bis(2,6-Dimethylphenyl)thiourea (6ap)**: White solid, m.p. 203–204 °C (water; ref.[91] 230–232 °C); $^1$H-NMR: (500 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.25−7.19 (m, 3H), 7.11−7.03 (m, 3H), 6.49 (bs, 1H), 2.45 (s, 3H), 2.24 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 180.9 (C), 137.7 (C), 136.5 (C), 135.7 (C), 133.2 (C), 129.3 (CH), 129.1 (CH), 128.3 (CH),


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128.1 (CH), 18.7 ($CH_3$), 18.3 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{21}N_2S$ 285.1419; found 285.1422.

**1-(2,6-Dimethylphenyl)-3-(4-methoxyphenyl)thiourea (6aq)**: Yellow solid, m.p. 147–148 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.64 (bs, 1H), 8.73 (bs, 1H), 7.31 (m, 2H), 7.07 (m, 3H), 6.91 (m, 2H), 3.74 (s, 3H), 2.20 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 181.0, 157.1, 136.8, 128.0 (bs), 114.5 (bs), 55.7, 18.5 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{19}N_2OS$ 287.1212; found 287.1217.

**1-(2,6-Dimethylphenyl)-3-(3,4,5-trimethoxyphenyl)thiourea (6ar)**: White solid, m.p. 170–171 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.78 (bs, 1H), 8.89 (bs, 1H), 7.08 (m, 3H), 6.82 (s, 2H), 3.76 (s, 6H), 3.65 (s, 3H), 2.21 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 179.8, 152.8 (bs), 137.4 (bs), 136.3, 134.6, 127.6 (bs), 126.7 (bs), 101.2 (bs), 60.0, 55.8, 18.1 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{23}N_2O_3S$ 347.1423; found 347.1435

**1-(4-Chlorophenyl)-3-(2,6-dimethylphenyl)thiourea (6as)**: Off white solid 136–137 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.93 (bs, 1H), 9.02 (bs, 1H), 7.55−7.27 (m, 4H), 7.09−7.06 (m, 3H), 2.20 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.3, 138.3, 136.3, 128.5 (bs), 128.3, 127.7 (bs), 126.8 (bs), 125.3, 124.7 (bs), 18.0 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{16}ClN_2S$ 291.0717; found 291.0725.

**1-(4-Bromophenyl)-3-(2,6-dimethylphenyl)thiourea (6at)**: Off white solid 128–129 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.91 (bs, 1H), 9.04 (bs, 1H), 7.52−7.45 (m, 5H), 7.09 (m, 3H), 2.21 (s, 3H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.8 (C), 139.2 (C), 136.8 (C), 131.7 (CH), 126.1 (CH), 117.0 (C), 18.5 ($CH_3$) ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{16}BrN_2S$ 335.0212; found 335.0212.

**1-(4-Iodophenyl)-3-(2,6-dimethylphenyl)thiourea (6au)**: Off white solid 159–160 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.93 (bs, 1H), 9.07 (bs, 1H), 7.66 (m, 2H), 7.40−7.34 (m, 2H), 7.09 (m, 3H), 2.20 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.2, 139.2, 137.1 (bs), 137.0, 136.2, 127.6 (bs), 126.8 (bs), 125.6, 125.1 (bs), 18.0 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{16}IN_2S$ 383.0073; found 383.0073.

**1-(2,6-Dimethylphenyl)-3-(4-hydroxyphenyl)thiourea (6av)**: White solid, m.p. 165–166 °C (water); $^1$H-NMR: (500 MHz, DMSO-$d_6$) δ 9.51 (bs, 1H), 9.33 (bs, 1H), 8.62 (bs, 1H), 7.16−7.06 (m, 4H), 6.74 (s, 2H), 2.19 (s, 6H) ppm; $^{13}$C-NMR: (125 MHz, DMSO-$d_6$) δ 180.4, 155.0, 136.4, 127.5 (bs), 126.5 (bs), 115.3 (bs), 18.0 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{17}N_2OS$ 273.1056; found 273.1062.

**Synthesis of 1-(isopentyloxy)-4-nitrobenzene (9)**: To the mixture of 4-nitrophenol (**7**, 4.17 g, 30 mmol), dimethylformamide (80 mL) and NaOH (3.60 g, 90 mmol), 1-bromo-3-methylbutane (**8**, 13.59 g, 90 mmol) was added, and the resulted mixture was refluxed for 3 hours. The solvent was evaporated and the residue was partitioned between diethyl ether (20 mL) and 1.0 M hydrochloric acid. The aqueous phase was extracted with diethyl ether (2× 20 mL), and the organic phases were combined. Evaporation of the solvent, followed by flash column chromatography on silica gel in hexane-ethyl acetate provided **9** in 70% yield (4.42 g). Brown oil; $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[92]) δ 8.18−8.15 (m, 2H), 6.94−6.91 (m, 2H), 4.07 (t, $J$=6.7 Hz, 2H), 1.86−1.80 (m, 1H), 1.70 (q, $J$=6.7 Hz, 2H), 0.97 (d, $J$=6.7 Hz, 6H) ppm.

**Synthesis of 4-(isopentyloxy)aniline (10)**: To the solution of 1-(isopentyloxy)-4-nitrobenzene (**9**, 4.19 g, 20 mmol) in ethyl acetate (80 mL), 10% Pd/C (0.2 mmol) was added and the resulting mixture was stirred under a hydrogen atmosphere of 4–7 bar for 1 hour. The reaction mixture was filtered through celite and the evaporation of the solvent provided **10** in quantitative yield (3.59 g). Brown oil; $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[92]) δ 6.74 (d, $J$=8.8 Hz, 2H), 6.64 (d, $J$=8.8 Hz, 2H), 3.92 (t, $J$=6.7 Hz, 2H), 3.40 (bs, 2H), 1.86−1.78 (m, 1H), 1.64 (q, $J$=6.8 Hz, 2H), 0.95 (d, $J$=6.6 Hz, 6H) ppm.

**Synthesis of *N*-(4-(isopentyloxy)phenyl)formamide (11)**: To formic acid (1.66 mL, 44 mmol) at 0 °C acetic anhydride (3.40 mL, 36 mmol) was added, then the mixture was heated up to 60 °C for 2 h. After cooling to 0 °C the reaction mixture was diluted with tetrahydrofuran (15 mL) and the solution of the amine **10** (1.79 g, 10 mmol) in tetrahydrofuran (15 mL) was added carefully. After the complete consumption of the amine followed by TLC, the volatiles were evaporated providing **11** in quantitative yield (2.07 g). Yellow oil; $^1$H-NMR: (500 MHz, $CDCl_3$, mixture of E/Z isomers) δ 8.51 (d, $J$=11.5 Hz, 0.46H), 8.35 (d, $J$=1.7 Hz, 0.54H), 7.44 (m, 1H), 7.03 (m, 1H), 6.91−6.87 (m, 2H), 4.00−3.97 (m, 2H), 1.88−1.81 (m, 1H), 1.71−1.66 (m, 2H), 0.99−0.97 (m, 6H) ppm; $^{13}$C-NMR: (125 MHz, $CDCl_3$) δ 158.6, 129.6, 121.9, 121.7, 117.0, 115.53, 114.9, 110.0, 66.7, 38.0, 25.1, 22.6 ppm; HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{18}NO_2$ 208.1332; found 208.1332.

**Synthesis of 1-isocyano-4-(isopentyloxy)benzene (12)**: To a solution of formamide **11** (1.66 g, 8 mmol) in tetrahydrofuran (10 mL) and triethylamine (8.92 mL, 64 mmol) was added phosphoryl chloride (1.50 mL, 16 mmol) dropwise at 0 °C. The resulted mixture was stirred under reflux until the consumption of **11** followed by TLC. Afterwards, aqueous sodium hydrogencarbonate (20 mL) was added slowly under ice cooling, then the reaction mixture was extracted with dichloromethane (2× 20 mL) and the organic layer was washed with brine (20 mL). Evaporation of the solvent followed by purification by flash column chromatography in hexane-ethyl acetate on aluminium oxide led to **12** in 73% yield (1.10 g). Green oil; $^1$H-NMR: (500 MHz, $CDCl_3$, ref.[93]) δ 7.28 (d, $J$=8.9 Hz, 2H), 6.85 (d, $J$=9.0 Hz, 2H), 3.99 (t, $J$=6.7 Hz, 2H), 1.86−1.78 (m, 1H), 1.68 (q, $J$=6.7 Hz, 2H), 0.97 (d, $J$=6.7 Hz, 6H) ppm.

**Synthesis of 1,3-bis(4-(isopentyloxy)phenyl)thiourea (Isoxyl®, thiocarlide, 13)**: 1-Isocyano-4-(isopentyloxy)benzene (**12**, 95 mg, 0.5 mmol) and 4-(isopentyloxy)aniline (**11**, 134 mg, 0.75 mmol) was added to the aqueous solution of sulfur and PMDTA (2.5 mL, 1.0 M PMDTA, 0.4 M sulfur) and stirred vigorously at 60 °C for 0.5 hour. After filtration of the reaction mixture, the solid was washed with water, then with 0.5 M hydrochloric acid, and finally with water to provide **13** in 84% yield (168 mg). Pale yellow solid, m.p. 136–137 °C (water; ref.[78] 139–141 °C, dichloromethane); $^1$H-NMR: (500 MHz, DMSO-$d_6$, ref.[78]) δ 9.39 (bs, 2H), 7.30 (d, $J$=8.4 Hz, 4H), 6.88 (d, $J$=8.5 Hz, 4H), 3.97 (t, $J$=6.4 Hz, 4H), 1.81−1.75 (m, 2H), 1.60 (q, $J$=6.4 Hz, 4H), 0.93 (d, $J$=6.5 Hz, 12H) ppm.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** sulfur · thiourea · chromatography-free · multicomponent reactions · water


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[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[2] W. Cao, F. Dai, R. Hu, B. Z. Tang, *J. Am. Chem. Soc.* **2020**, *142*, 978–986.
[3] L. Chen, P. Xia, T. Du, Y. Deng, Y. Xiao, *Org. Lett.* **2019**, *21*, 5529–5532.
[4] B. Phetsuksiri, M. Jackson, H. Scherman, M. McNeil, G. S. Besra, A. R. Baulard, R. A. Slayden, A. E. DeBarber, C. E. Barry, M. S. Baird, et al., *J. Biol. Chem.* **2003**, *278*, 53123–53130.
[5] S. Xiao, L. Wei, Z. Hong, L. Rao, Y. Ren, J. Wan, L. Feng, *Bioorg. Med. Chem.* **2019**, *27*, 805–812.
[6] J. Wu, Q. Shi, Z. Chen, M. He, L. Jin, D. Hu, *Molecules.* **2012**, *17*, 5139–5150.
[7] C. R. Worthing, R. J. Hance, British Crop Protection Council., *The Pesticide Manual: A World Compendium*, British Crop Protection Council **1991.**
[8] K. Biswas, M. F. Greaney, *Org. Lett.* **2011**, *13*, 4946–4949.
[9] J. Zhao, H. Huang, W. Wu, H. Chen, H. Jiang, *Org. Lett.* **2013**, *15*, 2604–2607.
[10] R. A. Batey, D. A. Powell, *Org. Lett.* **2000**, *2*, 3237–3240.
[11] S. M. Ghodse, V. N. Telvekar, *Tetrahedron Lett.* **2015**, *56*, 472–474.
[12] M. R. Maddani, K. R. Prabhu, *J. Org. Chem.* **2010**, *75*, 2327–2332.
[13] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.
[14] Á. Madarász, Z. Dósa, S. Varga, T. Soós, A. Csámpai, I. Pápai, *ACS Catal.* **2016**, *6*, 4379–4387.
[15] P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296.
[16] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[17] T. B. Nguyen, *Adv. Synth. Catal.* **2017**, *359*, 1066–1130.
[18] T. Chivers, P. J. W. Elder, *Chem. Soc. Rev.* **2013**, *42*, 5996–6005.
[19] A. G. Németh, G. M. Keserű, P. Ábrányi-Balogh, *Beilstein J. Org. Chem.* **2019**, *15*, 1523–1533.
[20] T. B. Nguyen, L. Ermolenko, P. Retailleau, A. Al-Mourabit, *Angew. Chem. Int. Ed.* **2014**, *53*, 13808–13812; *Angew. Chem.* **2014**, *126*, 14028–14032.
[21] H. Xie, J. Cai, Z. Wang, H. Huang, G.-J. Deng, *Org. Lett.* **2016**, *18*, 2196–2199.
[22] Y. Liao, Y. Peng, H. Qi, G. J. Deng, H. Gong, C. J. Li, *Chem. Commun.* **2015**, *51*, 1031–1034.
[23] J. Chen, G. Li, Y. Xie, Y. Liao, F. Xiao, G.-J. Deng, *Org. Lett.* **2015**, *17*, 5870–5873.
[24] Z. Chen, P. Liang, F. Xu, Z. Deng, L. Long, G. Luo, M. Ye, *J. Org. Chem.* **2019**, *84*, 12639–12647.
[25] M. Kozlov, A. Komkov, T. Losev, A. Tyurin, A. Dmitrenok, I. Zavarzin, Y. Volkova, *J. Org. Chem.* **2019**, *84*, 11533–11541.
[26] T. Szabó, M. Milen, *Chem. Heterocycl. Compd.* **2019**, *55*, 126–128.
[27] J. H. Boyer, V. T. Ramakrishnan, *J. Org. Chem.* **1972**, *37*, 1360–1364.
[28] A. Zajdlik, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer, A. K. Yudin, *Angew. Chem. Int. Ed.* **2013**, *52*, 8411–8415; *Angew. Chem.* **2013**, *125*, 8569–8573.
[29] W. Adam, R. M. Bargon, S. G. Bosio, W. A. Schenk, D. Stalke, *J. Org. Chem.* **2002**, *67*, 7037–7041.
[30] M. Arisawa, M. Ashikawa, A. Suwa, M. Yamaguchi, *Tetrahedron Lett.* **2005**, *46*, 1727–1729.
[31] W. S. Farrell, P. Y. Zavalij, L. R. Sita, *Organometallics.* **2016**, *35*, 2361–2366.
[32] S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal.* **2014**, *356*, 2135–2196.
[33] V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698–2779.
[34] S. ichi Fujiwara, T. Shin-Ike, K. Okada, M. Aoki, N. Kambe, N. Sonoda, *Tetrahedron Lett.* **1992**, *33*, 7021–7024.
[35] W. Feng, X. G. Zhang, *Chem. Commun.* **2019**, *55*, 1144–1147.
[36] T.-H. Zhu, X.-P. Xu, J.-J. Cao, T.-Q. Wei, S.-Y. Wang, S.-J. Ji, *Adv. Synth. Catal.* **2014**, *356*, 509–518.
[37] W. Tan, J. Wei, X. Jiang, *Org. Lett.* **2017**, *19*, 2166–2169.
[38] T. B. Nguyen, L. Ermolenko, A. Al-Mourabit, *Synth.* **2014**, *46*, 3172–3179.
[39] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.
[40] E. A. Peterson, B. Dillon, I. Raheem, P. Richardson, D. Richter, R. Schmidt, H. F. Sneddon, *Green Chem.* **2014**, *16*, 4060–4075.
[41] P. S. W. Leung, Y. Teng, P. H. Toy, *Org. Lett.* **2010**, *12*, 4996–4999.
[42] Z. Kaleta, G. Tárkányi, Á. Gömöry, F. Kálmán, T. Nagy, T. Soós, *Org. Lett.* **2006**, *8*, 1093–1095.
[43] P. A. Byrne, K. V. Rajendran, J. Muldoon, D. G. Gilheany, *Org. Biomol. Chem.* **2012**, *10*, 3531–3537.
[44] R. K. Orr, J. M. M. C. Dunn, A. Nolting, A. M. Hyde, E. R. Ashley, J. Leone, E. Sirota, J. A. Jurica, A. Gibson, C. Wise, et al., *Green Chem.* **2018**, *20*, 2519–2525.
[45] S. Tortoioli, A. Friedli, A. Prud'homme, S. Richard-Bildstein, P. Kohler, S. Abele, G. Vilé, *Green Chem.* **2020**, *22*.
[46] P. B. Thakur, H. M. Meshram, *RSC Adv.* **2014**, *4*, 5343–5350.
[47] C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82.
[48] A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725–748.
[49] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–164.
[50] M. B. Gawande, V. D. B. Bonifácio, R. Luque, P. S. Branco, R. S. Varma, *Chem. Soc. Rev.* **2013**, *42*, 5522–5551.
[51] P. Ábrányi-Balogh, T. Földesi, A. Grün, B. Volk, G. Keglevich, M. Milen, *Tetrahedron Lett.* **2016**, *57*, 1953–1957.
[52] M. Milen, P. Ábrányi-Balogh, A. Dancsó, D. Frigyes, L. Pongó, G. Keglevich, *Tetrahedron Lett.* **2013**, *54*, 5430–5433.
[53] P. Ábrányi-Balogh, A. Dancsó, D. Frigyes, B. Volk, G. Keglevich, M. Milen, *Tetrahedron.* **2014**, *70*, 5711–5719.
[54] V. Varga, M. Milen, P. Ábrányi-Balogh, *Tetrahedron Lett.* **2018**, *59*, 3683–3689.
[55] P. Ábrányi-Balogh, B. Volk, M. Milen, *Tetrahedron Lett.* **2018**, 617–619.
[56] E. Davis, *J. Am. Chem. Soc.* **1962**, *84*, 2085–2090.
[57] T. A. Tikhonova, K. A. Lyssenko, I. V. Zavarzin, Y. A. Volkova, *J. Org. Chem.* **2019**, *84*, 15817–15826.
[58] P. Yu, Y. Wang, Z. Zeng, Y. Chen, *J. Org. Chem.* **2019**, *84*, 14883–14891.
[59] J. Liu, Y. Zhang, Y. Yue, Z. Wang, H. Shao, K. Zhuo, Q. Lv, Z. Zhang, *J. Org. Chem.* **2019**, *84*, 12946–12959.
[60] L. Gan, Y. Gao, L. Wei, J.-P. Wan, *J. Org. Chem.* **2019**, *84*, 1064–1069.
[61] M. Wu, Y. Jiang, Z. An, Z. Qi, R. Yan, *Adv. Synth. Catal.* **2018**, *360*, 4236–4240.
[62] S. Shi, J. Chen, S. Zhuo, Z. Wu, M. Fang, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2019**, *361*, 3210–3216.
[63] M. Kozlov, A. Kozlov, A. Komkov, K. Lyssenko, I. Zavarzin, Y. Volkova, *Adv. Synth. Catal.* **2019**, *361*, 2904–2915.
[64] X. Zhang, Z. Shi, C. Shao, J. Zhao, D. Wang, G. Zhang, L. Li, *Eur. J. Org. Chem.* **2017**, *2017*, 1884–1888.
[65] Y. Zhang, Y. Liu, J. Zhang, R. Gu, S. Han, *Tetrahedron Lett.* **2019**, *60*, 151289.
[66] Z. Wang, C. Zhang, H. Wang, Y. Xiong, X. Yang, Y. Shi, A. L. Rogach, *Angew. Chem. Int. Ed.* **2020**, *59*, 1–7.
[67] J. W. Thomson, K. Nagashima, P. M. Macdonald, G. A. Ozin, *J. Am. Chem. Soc.* **2011**, *133*, 5036–5041.
[68] D. Peixoto, G. Malta, H. Cruz, S. Barroso, A. L. Carvalho, L. M. Ferreira, P. S. Branco, *J. Org. Chem.* **2019**, *84*, 3793–3800.
[69] M. Vangala, G. P. Shinde, *Beilstein J. Org. Chem.* **2016**, *12*, 2086–2092.
[70] R. Nirmala, T. Ponpandian, B. R. Venkatraman, S. Rajagopal, *Tetrahedron Lett.* **2013**, *54*, 5181–5184.
[71] H. Lammers, P. Cohen-Fernandes, C. L. Habraken, *Tetrahedron.* **1994**, *50*, 865–870.
[72] S. B. Baravkar, A. Roy, R. L. Gawade, V. G. Puranik, G. J. Sanjayan, *Synth. Commun.* **2014**, *44*, 2955–2960.
[73] N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou, B. H. Lipshutz, *Org. Lett.* **2015**, *17*, 4734–4737.
[74] R. S. Gonçalves, P. V. Abdelnur, V. G. Santos, R. C. Simas, M. N. Eberlin, A. Magalhães, E. R. Pérez González, *Amino Acids.* **2011**, *40*, 197–204.
[75] B. Gierczyk, G. Schroeder, B. Brzezinski, *J. Org. Chem.* **2003**, *68*, 3139–3144.
[76] O. A. Shemyakina, O. G. Volostnykh, A. V. Stepanov, A. G. Mal'Kina, I. A. Ushakov, B. A. Trofimov, *Synth.* **2018**, *50*, 853–858.
[77] V. Bhowruth, A. K. Brown, R. C. Reynolds, G. D. Coxon, S. P. Mackay, D. E. Minnikin, G. S. Besra, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4743–4747.
[78] J. R. Brown, E. J. North, J. G. Hurdle, C. Morisseau, J. S. Scarborough, D. Sun, J. Korduláková, M. S. Scherman, V. Jones, A. Grzegorzewicz, et al., *Bioorg. Med. Chem.* **2011**, *19*, 5585–5595.
[79] R. Pingaew, V. Prachayasittikul, N. Anuwongcharoen, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittikul, *Bioorg. Chem.* **2018**, *79*, 171–178.
[80] K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya, T. Doi, *Adv. Synth. Catal.* **2010**, *352*, 2643–2655.
[81] T. T. Li, X. H. Song, M. S. Wang, N. Ma, *RSC Adv.* **2014**, *4*, 40054–40060.
[82] P. K. Mohanta, S. Dhar, S. K. Samal, H. Ila, H. Junjappa, *Tetrahedron.* **2000**, *56*, 629–637.
[83] R. Custelcean, M. G. Gorbunova, P. V. Bonnesen, *Chem. Eur. J.* **2005**, *11*, 1459–1466.
[84] B. Loev, P. E. Bender, H. Bowman, A. Helt, R. Mclean, T. Jen, *J. Med. Chem.* **1972**, *15*, 1024–1027.
[85] M. E. Jung, B. T. Chamberlain, C. L. C. Ho, E. J. Gillespie, K. A. Bradley, *ACS Med. Chem. Lett.* **2014**, *5*, 363–367.


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[86] H. Martin, D. Dürr, A. Hubele, O. Rohr, J. Rufener, G. Pissiotas, *Verfahren Und Mittel Zur Förderung Der Fruchtabszission*, Patent number CH560003 (A5), **1975**.
[87] Kanwal, M. Khan, Arshia, K. M. Khan, S. Parveen, M. Shaikh, N. Fatima, M. I. Choudhary, *Bioorg. Chem.* **2019**, *83*, 595–610.
[88] B. V. Varun, K. R. Prabhu, *RSC Adv.* **2013**, *3*, 3079–3087.
[89] T. Jen, H. Hoeven Van, W. Groves, R. A. McLean, B. Loev, *J. Med. Chem.* **1975**, *18*, 90–99.
[90] L. Krasovskiy, Arkady, E. Szuromi, *Thioguanidine Group IV Transition Metal Catalysts and Polymerization Systems*, Patent number US 2019/0263949 A1, **2019**
[91] S. Sakai, T. Fujinami, T. Aizawa, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 425–428.
[92] A. Liav, S. K. Angala, P. J. Brennan, *Synth. Commun.* **2008**, *38*, 1176–1183.
[93] K. K. Kenichi Eguchi, Akira Ohira, Yoshikazu Kitano, *Marine Sessile Organism-Repelling Composition*, Patent number US 2018/0072657 A1, **2018**.

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