

Chromatography-free multicomponent synthesis of thioureas with aqueous polysulfide solutions under batch and continuous flow conditions

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Abstract

We have developed a batch and continuous flow (CF) process for the three-component chromatography-free synthesis of thioureas starting from isocyanides, amidines or amines, and elemental sulfur in water. First, screening a large pool of organic and inorganic bases, we realized the preparation of aqueous polysulfide solutions from elemental sulfur. These solutions facilitated the separation of the excess of sulfur from the crystallized products by a simple filtration, retaining sulfur in the mother liquid. This approach enabled us to tackle the otherwise mandatory chromatographic purification in sulfur-based reactions. Moreover, applying polysulfide solutions, we carried out the convenient CF application of sulfur. Presenting thioureas of a broad variety synthesized by this procedure, highlighting challenging *N,N'*-diaryl derivatives, confirms the reasonable substrate and functional group tolerance of the developed protocol.

Keywords: *multicomponent reaction; sulfur; thiourea; chromatography-free, continuous flow*

Introduction and Objectives

Sulfur-containing compounds, such as thioureas, are widely known as biologically active molecules [1] and functional organic materials [2]. Notably, in the last two decades, thioureas were also applied as highly selective and efficient organocatalysts [3]. 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 offering an atom economical and safe alternative to incorporate the sulfur atom into products [4]. Certain nucleophiles, such as aliphatic amines, can generate open-chain ionic polysulfide anions from elemental sulfur [5], resulting in an efficient nucleophilic sulfurating reagent. In the last two decades, CF synthesis has become a powerful and versatile tool in synthetic organic chemistry. The main advantages of that approach are facile automation, reproducibility, safety, and process reliability, because constant reaction parameters (temperature, time, concentrations etc.) can be assured [6]. The CF techniques are suitable for multistep [7] and automated synthetic processes, which is a burgeoning and exciting area of research [8]. In the past decade, a couple of innovative, multicomponent and one-pot procedures have been published for the use of

elemental sulfur in synthetic procedures leading to the formation of thioureas [9]. However, the excess of sulfur makes chromatography indispensable as crystallization from an organic solvent is not suitable for removing sulfur. Moreover, the convenient preparation of *N,N'*-diaryl thioureas remained a challenge due to the reduced nucleophilic behavior of aromatic amines.

In continuation of our interest in green chemistry [10], multicomponent reactions [11] and reactions involving sulfur [5], we aimed to prepare aqueous solution of polysulfide anions to use it as a novel sulfurating reagent. The application of this reagent offers an environmentally friendly and atom economical access to thio compounds in water with easy work-up and the potential to develop chromatography-free synthetic methods. Moreover, with its use, we intended to introduce sulfur into CF reactors. As a proof of concept approach, herein we present the novel efficient synthesis of diversely substituted thioureas in water under batch and CF conditions [12,13] from isocyanides and amines.

Materials and methods

Reaction course and the total consumption of the isocyanide were monitored by HPLC-MS at 190 nm wavelength. HPLC-MS measurements were performed using a Shimadzu LCMS-2020 device equipped with a Reprospher 100 C18 (5 μ m; 100 $\times$ 3 mm) column and positive-negative double ion source (DUIS $\pm$) with a quadrupole MS analyzer in a range of 50–1000 *m/z*. New compounds were characterized by ^1H NMR and ^{13}C NMR, HRMS, and if were obtained in solid form by melting point. ^1H and ^{13}C NMR spectra were recorded in DMSO-*d*₆ or CDCl₃ solution at room temperature, on a Varian Unity Inova 500 spectrometer (500 and 125 MHz for ^1H and APT NMR spectra, respectively), with the residual solvent signal as the lock and TMS as the internal standard. In the CF system, the stream of the solution of the starting materials was provided by HPLC pumps (JASCO model PU–2080), and the tubing (BGB, 1/16" OD $\times$ 0.50 mm or 1.00 mm ID, 10 m) was placed in a Carlo Erba HRGC 5300 oven.

Results and discussion

Our first objective was to prepare polysulfide anion containing aqueous solutions from sulfur using 36 different bases (Tab. 1.). We found 14 bases suitable for this purpose at a concentration of at least 0.05 M with respect to sulfur that is perfectly suited for synthetic applications [14]. Generally, inorganic bases, piperidine and, 1,4-diazabicyclo[2.2.2]octane (DABCO) were suitable for preparing diluted, 0.05 M or 0.1 M solution of sulfur (entries 1–4 and 11). Considering amidines and other tertiary amines, we successfully prepared more

concentrated 0.4 M solutions of sulfur in the presence of only 2.5 equivalents of base (entries 5–10). In a few cases, the addition of 50% co-solvent was necessary to keep the bases in solution (entries 12–14). Although in the presence of certain bases we reached higher concentrations, for practical considerations (versatility, comparability and easy-handling), we have standardized the amount of base and elemental sulfur at 1.0 M and 0.4 M. We investigated the role of organic bases in the preparation of polysulfide solutions by ^1H NMR in D_2O . We proved the quaternization of certain nitrogen atoms, confirming the nucleophilic attack of the base on sulfur. In the case of cyclic amidines we observed their literature known autocatalyzed ring-opening hydrolysis yielding lactams and pyrimidinones equipped with a primary aliphatic amino group [15]. These primary amines are responsible for the fast and convenient preparation of the polysulfide solutions.

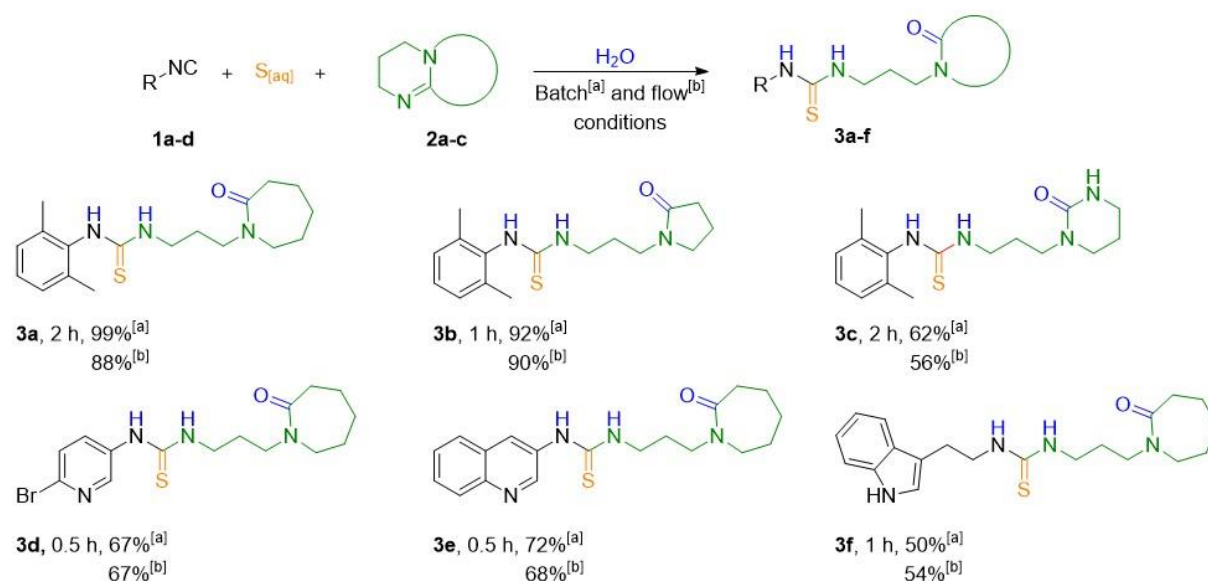
Tab. 1. Suitable bases for the preparation of aqueous polysulfide solution

Entry ^[a]	Base	Base/S ₈ concentration ^[b]	Entry ^[a]	Base	Base/S ₈ concentration ^[b]
1	NaOH	1.0 M/0.05 M	8	MTBD	1.0 M/0.4 M
2	Na ₂ S	1.0 M/0.05 M	9 ^[c,d]	PMDTA	1.0 M/0.4 M
3	TBAOH	1.0 M/0.05 M	10 ^[d]	DIPA	1.0 M/0.4 M
4	Piperidine	1.0 M/0.05 M	11 ^[d]	DABCO	1.0 M/0.1 M
5	DBU	1.0 M/0.4 M	12 ^[d,e]	Triethylamine	1.0 M/0.4 M
6	DBN	1.0 M/0.4 M	13 ^[d,e]	N-Ethylpiperidine	1.0 M/0.4 M
7	TBD	1.0 M/0.4 M	14 ^[d,f]	Quinine	0.25 M/0.15 M

^[a] Conditions: 60 °C, water, vigorous stirring, 2 h. ^[b] Concentration of base and sulfur respectively. ^[c] 70 °C was employed. ^[d] Overnight stirring was employed. ^[e] 50% acetonitrile was used as co-solvent. ^[f] 50% THF was used as co-solvent. TBOH: tetrabutylammonium hydroxide, DBN: 1,5-diazabicyclo[4.3.0]non-5-ene, TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene, MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene PMDTA: *N,N,N',N'',N'''*-pentamethyldiethylenetriamine, DIPA: diisopropylamine.

We envisioned the reaction of the polysulfide solution of amidines **2a–c** (Scheme 1) with isocyanides **1a–d** in order to generate caprolactam and piperidinone substituted thioureas **3a–f**. We found this reaction suitable for the validation of the aqueous polysulfide solution to prepare isothiocyanate from isocyanide (**1a–d**) followed by the transformation to thiourea (**3a–f**) in a one-pot, multicomponent manner. We optimized the reaction conditions in batch (temperature, time, molar excess of reagents) and in CF reactor (temperature, flow rate, residence time) as well. After complete conversion of the isocyanide monitored by HPLC-MS, the pure crystalline product was isolated by filtration, and the excess of polysulfide solution and amine was washed away by water. In the CF system, it was necessary to use acetonitrile as co-solvent to keep the components in solution and avoid clogging. After collecting the product mixture, we removed the co-solvent in vacuo, and isolated the crystalline product by filtration. We have applied the optimized reaction conditions to a structurally diverse set of amidines and

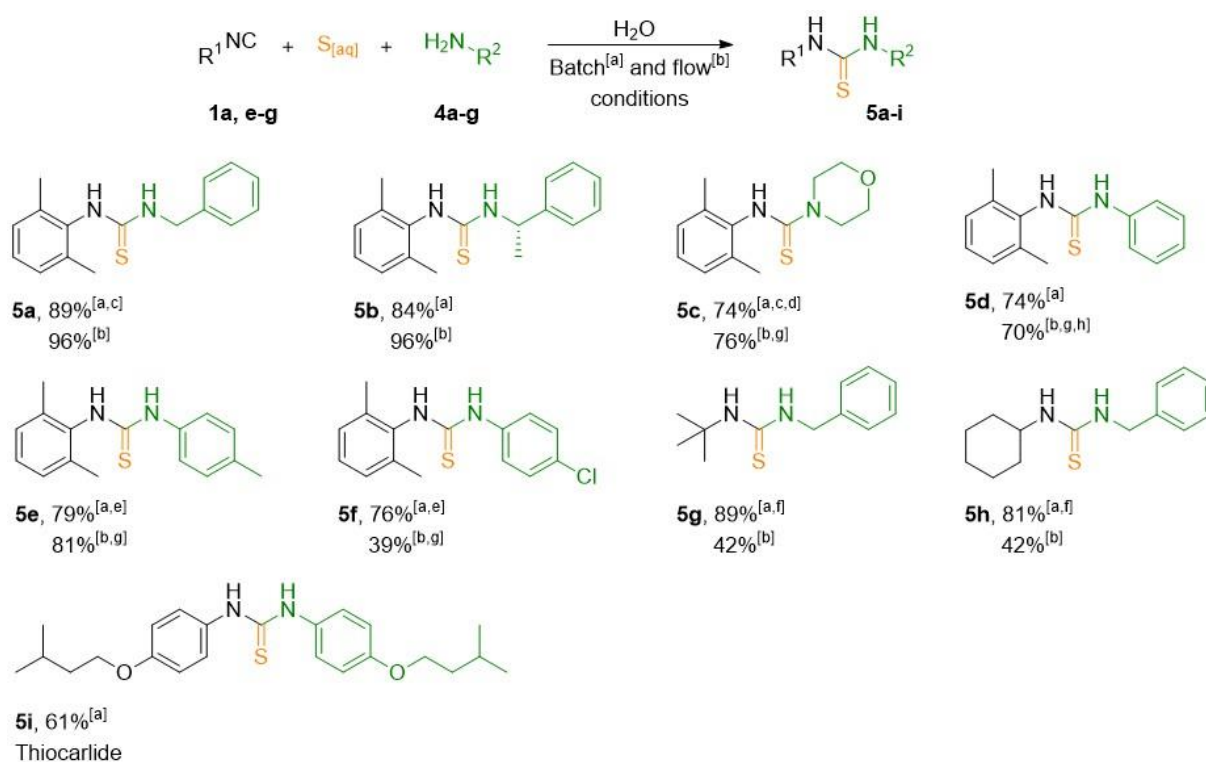
isocyanides to investigate the scope and limitation of the developed method.



Scheme 1. Substrate scope of amidines and isocyanides

Isolated yields shown at 0.5 mmol respective to isocyanide **1a-d**; ^[a] Batch reaction conditions: **1a-d** (0.50 mmol), polysulfide solution (1.0 M **3a-c** base/0.4 M S_[aq], 2.5 mL), 60 °C, reaction time and isolated yield on the scheme. ^[b] CF conditions: **1a-d** (0.2 M in acetonitrile), polysulfide solution (1.0 M **3a-c**/0.4 M sulfur in water), 80 °C, 6.5 min residence time, 0.3 mL min⁻¹ flow rate.

Polysulfide solutions made with bases resistant to acylating agents such as DABCO, PMDTA, triethylamine, *N*-ethylpiperidine, and quinine (Tab. 1), enables the preparation of virtually any desired thioureas (Scheme 2). Applying a diverse set of isocyanides and aliphatic and aromatic amines, we investigated the generality of the reaction using the polysulfide solution made with PMDTA (1.0 M) and sulfur (0.4 M, Tab. 1, entry 9). We used this simple method efficiently for the preparation of *N,N'*-diaryl thioureas and derivatives containing a heterocyclic scaffold or aromatic halogen atoms. The two approaches provided the thioureas in similar yields (**5c–5e**), however, in some cases, we observed a significant difference between the two protocols either in favor of the batch (**5f–5h**) or the CF (**5a**, **5b**) reaction setup. Interestingly, we have not recognized any clear effect yet that may help to predict the relation between the experimental protocol and the structure of the substrates. As an eye-catching example, we synthesized the marketed, antitubercular drug thiocarlide (Isoxyl[®]) in batch [16]. In conclusion, our method has provided better overall yield (61% for 4 steps) for the synthesis of thiocarlide compared to published procedures using poisonous carbon disulfide (53%)[17] or highly toxic thiophosgene (50%)[18] as sulfur sources.



Scheme 2. Substrate scope for amines and isocyanides, and the marketed drug example

^[a] Batch reaction conditions: **1a, e-g** (0.50 mmol), **4a-g** (0.75 mmol), polysulfide solution (1.0 M PMDTA/0.4 M S_[aq], 2.5 mL), 60 °C, 0.5 h and isolated yield in the figure. ^[b] Continuous flow conditions: isocyanide **1a, e-g** and amine **4a-g** (0.2 M isocyanide and 0.3 M amine in acetonitrile), polysulfide solution (1.0 M PMDTA/0.4 M sulfur in water), 80 °C, 6.5 min residence time, 0.3 mL min⁻¹ flow rate, isolated yield 0.5 mmol scale in the figure. ^[c] 80 °C. ^[d] 3 equivalents of **4c**. ^[e] 1 h reaction time. ^[f] 2 h reaction time. ^[g] 0.6 M for the amine in acetonitrile ^[h] 2-Methyltetrahydrofuran was used as co-solvent instead of acetonitrile.

Conclusion

In summary, we have prepared aqueous solutions of polysulfide anions from sulfur using a large pool of organic and inorganic bases. We used the resulting aqueous solutions in the efficient, chromatography-free multicomponent synthesis of thioureas 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-, tetrahydropyrimidin-2-one and other, disubstituted thioureas, highlighting *N,N'*-diaryl derivatives and the marketed drug, thiocarlide. Applying polysulfide solutions, we have shown the convenient application of sulfur under CF conditions and investigated the scope and limitations of the developed procedure.

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