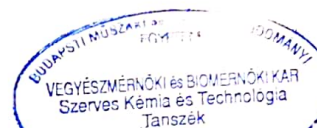




Chromatography-free multicomponent synthesis of thioureas with aqueous polysulfide solutions under batch and continuous flow conditions

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Introduction

Elemental sulfur-based multicomponent reactions are significant and efficient methods in modern synthetic chemistry due to their ability to produce complex sulfur-containing structures, even in one technological step, or to provide environmentally friendly, atom economic, and safe alternative to existing synthetic procedures [1-2].

In the last two decades, continuous flow (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 can be assured [3].

We aimed to prepare aqueous solution of polysulfide anions using water soluble bases starting from sulfur to use it as a novel sulfuring reagent. The application of this reagent offers an efficient access to thioureas from isocyanides and amidines or amines in water with easy work-up and the potential to develop chromatography-free synthetic methods [4]. Moreover, we intended to introduce sulfur into CF reactors [5].

Polysulfide solutions

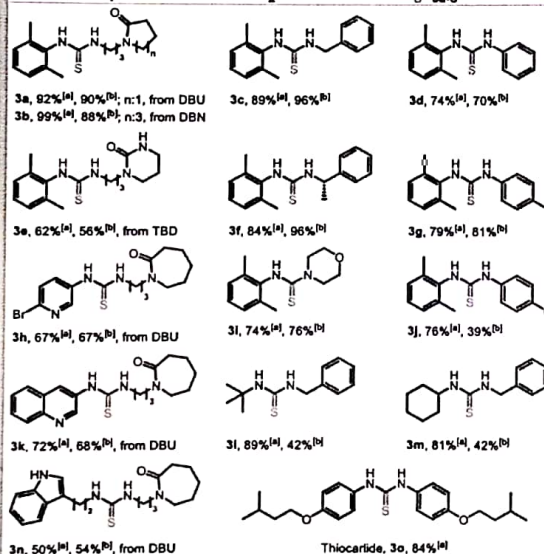
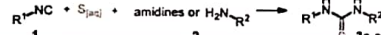
Considering the ionic structure of the chemically reactive polysulfide chain, we envisioned its aqueous solution as a new sulfuring reagent. Eventually, from the 36 screened bases in water or aq. solvent mixtures 14 were found suitable for the preparation of aqueous polysulfide solutions. For practical considerations, we have standardized concentration of base (Table 1) and sulfur at 1.0 M and 0.4 M. In the case of cyclic amidines, we observed their ring-opening hydrolysis yielding lactams and pyrimidones equipped with primary aliphatic amino group.

Amidines	Tertiary, secondary amines
DBU, DBN, TBD, MTBD	PMDTA
	Triethylamine
	N-Ethylpiperidine
	DIPA

Table 1. Examples of bases for the preparation of aqueous polysulfide solutions with standardized concentrations

Chromatography-free synthesis

These aqueous polysulfide solutions were used efficiently for the chromatography-free multicomponent synthesis of thioureas in good to excellent yields. The methodology has been validated in a wide range of synthesis scenarios, including challenging *N,N'*-diaryl derivatives and the marketed drug, Thiocarlide (Scheme 1). This approach enables the easy isolation of the desired products by a simple filtration, retaining the excess of sulfur in the solution phase. We optimized the reaction conditions in batch and in CF reactor as well.

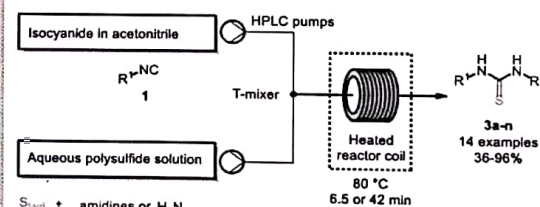
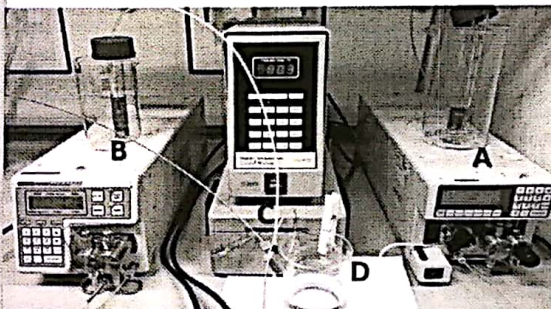


Scheme 1. Representative examples for the chromatography-free multicomponent synthesis of thioureas using aqueous polysulfide solutions

^[a] Batch: 1 (0.5 mmol), S_8 (1.0 mmol), 2 (2.5 mmol), 60–80 °C, water, 0.5–4 h.
^[b] CF conditions: 1 (0.2 M), S_8 (0.4 M), 2 (1.0 M), 80 °C, water:MeCN 1:1, t_R = 6.5 min.

Flow system

Performing the synthesis of thioureas (Scheme 2) in a 1:1 mixture of water and acetonitrile kept both the polysulfide anions and the apolar compounds in solution. We applied two HPLC pumps to provide the feed for the aqueous polysulfide solution (Scheme 2, A), and the solution of the isocyanide in acetonitrile (Scheme 2, B). Water-soluble amines were dissolved in feed A, otherwise in feed B. The two inputs met in a T-mixer right before the heated reactor oven (Scheme 2, C), and the output was collected in a flask (Scheme 2, D).



Scheme 2. Experimental setup of the CF system

After completion of the reaction, removal of the acetonitrile in vacuo resulted in the precipitation of the product which could be separated easily by filtration retaining the excess of sulfur in solution.

Conclusion



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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List of abbreviations

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene, DBN: 1,5-diazabicyclo[4.3.0]non-5-ene, TB: 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'*-pentamethyldiethylenetriamine, DIPA: diisopropylamine.

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A dokumentum hitelességét igazolom.
Kucser József