

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 S₈.

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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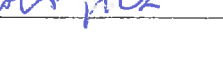
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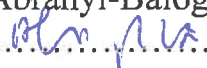
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