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FULL PAPER

Convenient multicomponent one-pot synthesis of 2-iminothiazolines and 2-aminothiazoles using elemental sulfur under aqueous conditions

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Dedicated to professor Ferenc Fülöp on the occasion of his 70th birthday.

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Abstract: Herein, we present a novel one-pot aqueous reaction for the synthesis of 2-iminothiazolines and 2-aminothiazoles using isocyanides, amines, sulfur and 2′-bromoacetophenones. The three-component preparation of thioureas is followed one-pot by the cyclization leading to the heterocycle. This efficient and mild procedure features excellent step– and atom–economy and enables the chromatography–free preparation of diversely substituted 2-iminothiazoline and 2-aminothiazole derivatives.

Introduction

2-Iminothiazolines are biologically active compounds represented by selective cannabinoid receptor type 2 (CB2) agonists,[1–4] carbonic anhydrase (CA), cyclooxygenase (COX) and lipoxygenase (LOX) inhibitors,[5–9] anticancer [10,11] and antithrombotic agents, [12] HIV1 reverse transcriptase inhibitors [13] and fungicides (Figure 1).[14] Similarly, related 2-aminothiazoles showed anticancer,[15–18] antibacterial,[19] anticonvulsant, antidiabetic, antihypertensive, anti-inflammatory, antiviral, antimicrobial and neuroprotective activities.[20] They are represented by the marketed antiviral and antiparasitic drug Nitazoxanide, the β3 adrenergic receptor agonist Mirabegron, the antileukemic Dasatinib and the antiulcer Famotidine (Figure 1).[21] The significance of the 2-iminothiazoline and 2-aminothiazole structures calls for new and efficient synthetic methods, which offer simple and convenient access towards diverse functionalization patterns. Also, the environmental aspects of the synthesis, e.g. the application of less toxic solvents, exclusion of chromatographic purification and simple isolation of the desired products should be considered.[22,23] Water is an ideal non-toxic, abundant and cheap medium that offers a simple isolation protocol of apolar products as a main advantage.[24–27]

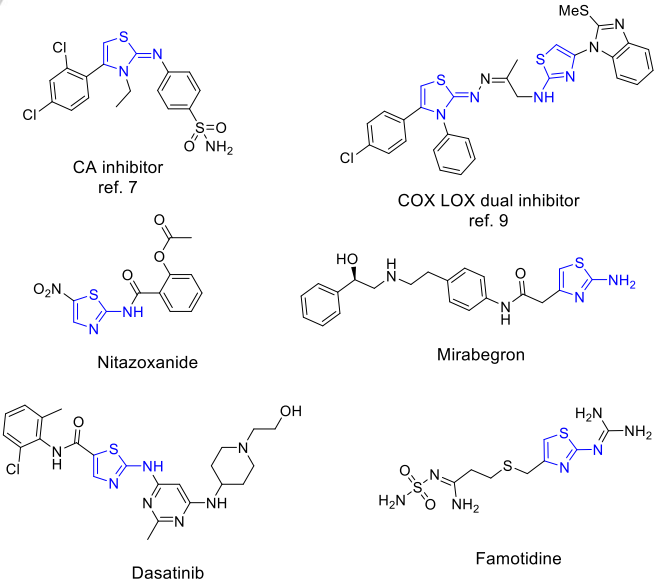
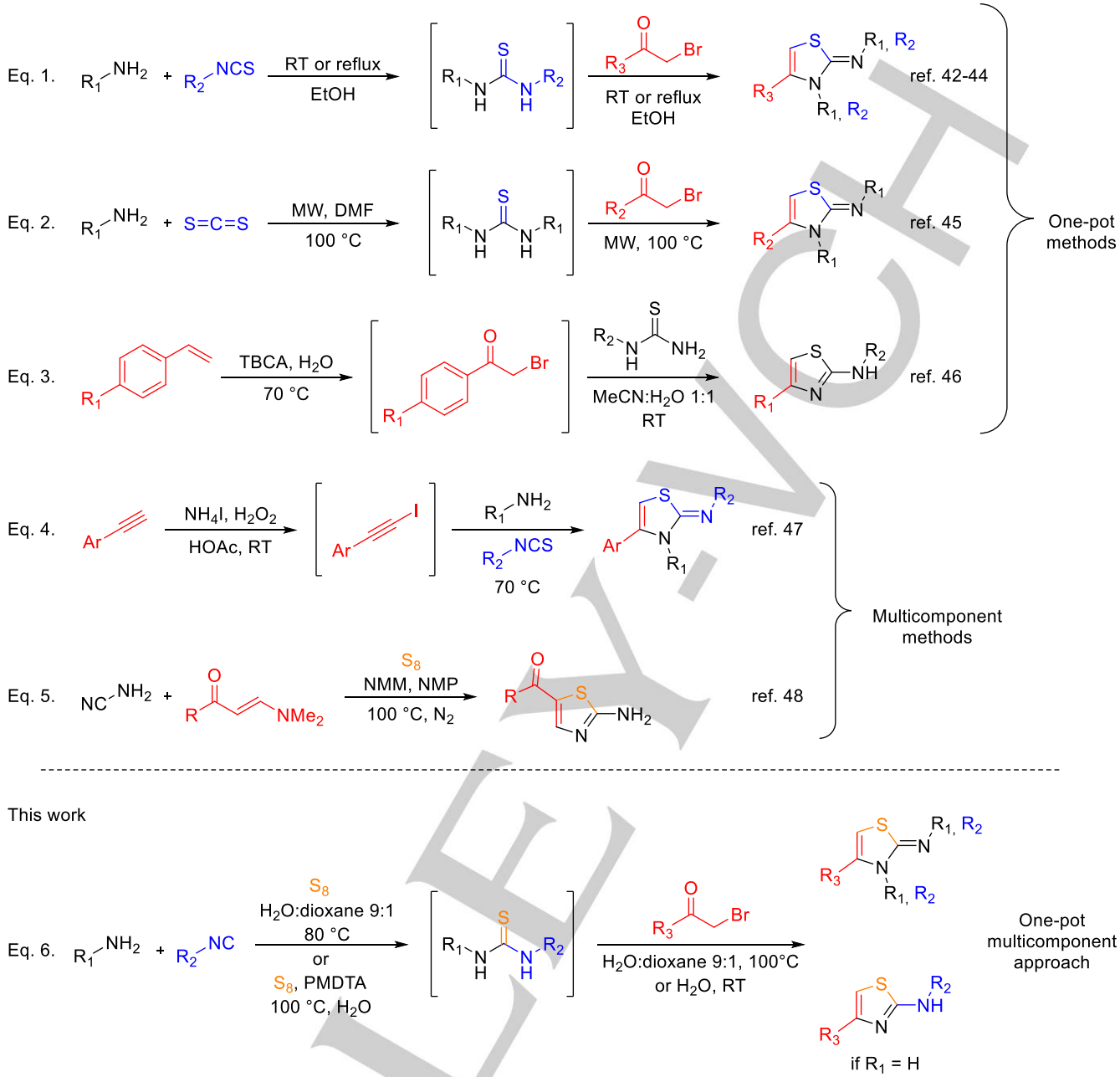


Figure 1. Examples of biologically active 2-iminothiazolines and 2-aminothiazoles



Scheme 1. Previous one-pot and multicomponent approaches for the synthesis of 2-iminothiazolines, 2-aminothiazoles and this work

Chromatographic purification produces large waste of organic solvents and dischargeable solid phase, thus, the improvement of existing synthetic methods to avoid chromatography remains an important issue.[23,28–33]

The traditional Hantzsch thiazole synthesis starts from thioureas and α-haloketones [34,35]. Unsubstituted and *N*-monosubstituted thioureas lead to 2-aminothiazoles while *N,N'*-disubstituted ones lead to 2-iminothiazolines. The regioselectivity is driven by the pK_a values of the NH protons, particularly the more basic nitrogen participates in the formation of the heterocycle.[14,36,37] Several variant of the original synthetic method have been developed, like solid supported synthesis [14,38] base-catalyzed and aqueous methods.[39–41] Considering green chemistry principles and synthetic efficiency, we focused on one-pot and multicomponent approaches that have been designed by the *in situ* synthesis of thioureas or α-haloketones. *Raja et al*., *Samimi et al.* and *Heravi et al.* reported the preparation of 2-iminothiazolines in one-pot, based on the *in situ* generation of thioureas from amines and isothiocyanates followed by the ring annulation with 2'-bromoacetophenones (Scheme 1, eq. 1).[42–44] *Appalanaidu et al.* applied carbon disulfide in the microwave assisted preparation of symmetrical thioureas in the one-pot synthesis of 2-iminothiazolines (Scheme 1, eq. 2).[45] Notably, *De Andrade et al.* published a tribromoisocyanuric acid (TBCA) mediated approach

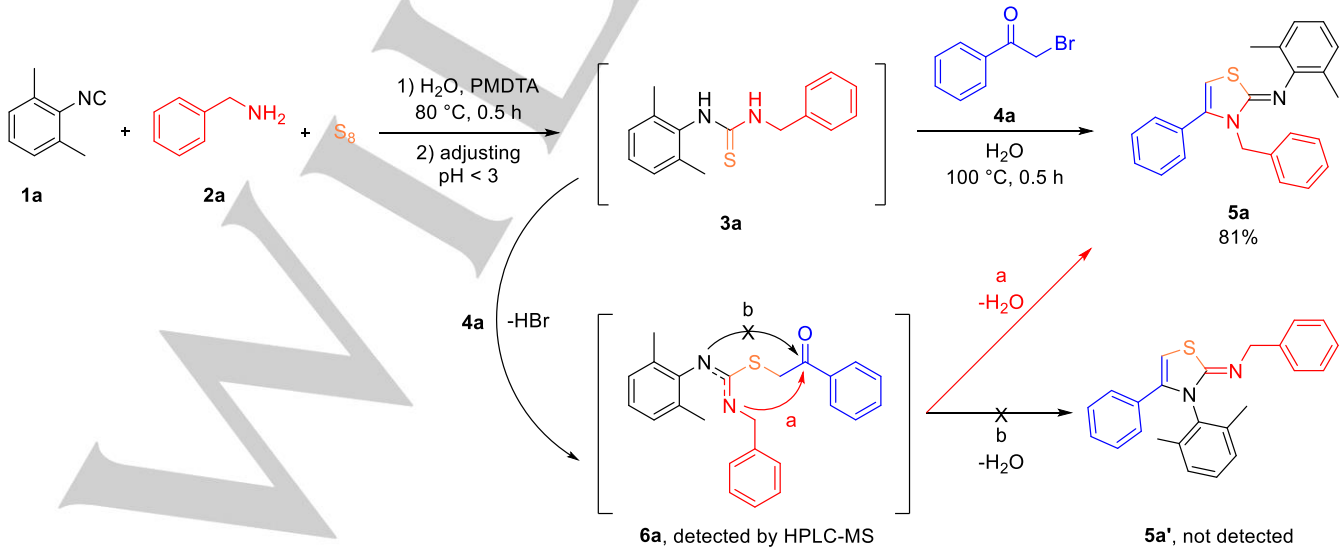
for the *in situ* synthesis of 2'-bromoacetophenones which they sequentially reacted with thioureas to obtain 2-aminothiazoles (Scheme 1, eq. 3).[46] Recently, *Kumar et al.* developed multicomponent method using *in situ* peroxide-generated aryl iodoalkynes for the ring annulation (Scheme 1, eq. 4).[47] Finally, *Fu et al.* synthesized 5-acyl-2-aminothiazoles starting from enaminones, sulfur and cyanamide in a multicomponent reaction (Scheme 1, eq. 5).[48] Although these approaches provided the desired products efficiently, they have limited substrate scope. Furthermore, they either enable the generation of only symmetrical thioureas or require the preparation and handling of highly toxic isothiocyanate intermediates (Scheme 1, eq. 1, 2 and 4). Other approaches offer one or two positions of variability, thus benefit merely from a limited chemical space (Scheme 1, eq. 3 and 5). Moreover, the application of toxic and hazardous solvents or inert conditions and long reaction times urges for the development of an all-purpose and convenient synthetic procedure leading to structurally diverse 2-iminothiazolines and 2-aminothiazoles.

Elemental sulfur is a bench-stable environmentally benign, nontoxic reagent for sulfuration offering an atom-economical and safe alternative to incorporate the sulfur atom.[49–52] Although plenty of sulfurating reagents are available, the application of elemental sulfur is considered to the most atom economical approach.[53] Certain nucleophiles, such as aliphatic amines are able to activate sulfur, generating open-chain ionic polysulfide anions which can be used in the atom efficient sulfuration of isocyanides leading to isothiocyanates.[54–57] Recently, we have published the preparation of aqueous solutions of sulfur that we applied in the chromatography–free and continuous flow synthesis of thioureas starting from isocyanides and both aliphatic and aromatic amines.[54,56] These methodologies enable the synthesis of symmetric or asymmetric thioureas from the isothiocyanate precursor isocyanides and the isolation of the pure products by a simple filtration. In continuation of our interest in multicomponent reactions[58–60] and reactions involving elemental sulfur[54–56,61] we have aimed to further elaborate the application of aqueous polysulfide solutions. Herein we present the multicomponent one-pot synthesis of diverse 2-iminothiazolines and 2-aminothiazoles starting from isocyanides, sulfur, amines, and 2′-bromoacetophenones (Scheme 1, eq. 6).

Results and Discussion

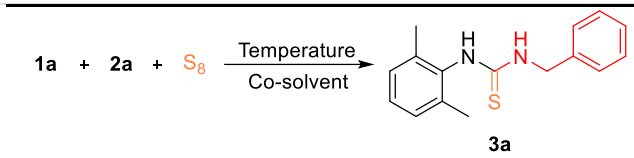
Starting from 2,6-dimethylphenyl isocyanide (**1a**), benzylamine (**2a**) and the aqueous polysulfide solution made of 1.0 M PMDTA and 0.4 M sulfur, we synthesized the thiourea **3a** at 80 °C in 0.5 hour through an isothiocyanate intermediate detected by HPLC-MS.[54–56] Next, we did not isolate **3a**, but aimed to transform it using 2'-bromoacetophenone (**4a**) to the corresponding iminothiazoline **5a**. Under basic conditions, however, the ring annulation with **4a** could not reach full conversion, a mixture of the product **5a** and the intermediate **6a** could be observed in HPLC-MS. Therefore, we decided to acidify the reaction mixture to pH < 3 with cc aq. HBr to have the same anion present as the leaving group from **4a**. Then, we added 2'-bromoacetophenone (**4a**) and continued the reaction at 100 °C that temperature was necessary for the cyclization.[49,62] After 0.5 hour, we observed the total consumption of the *in situ* generated thiourea by HPLC-MS. The hydrogen bromide salt of **5a** precipitated from the reaction mixture, which we isolated by filtration and washed with 1.0 M aq. NaOH and water providing **5a** in 81% yield (Scheme 2). Thus, to our delight, starting from simple building blocks we have obtained the desired 2,3,4-trisubstituted iminothiazoline **5a** in a one-pot two–step synthesis without applying chromatographic purification. Although the ring-closure may lead to the regioisomer **5a'**, we did not observed its formation in the reaction. Presumably the significant difference between the pK_a values of benzylamine and 2,6-dimethylaniline enables the regioselective preparation of **5a**.[14,36,37]

The nucleophilic character of aliphatic amines such as phenethylamine, or benzylamine [63] are able to activate sulfur that might provide **3a** and then **5a** in the absence of external bases. The reaction of **1a**, **2a** and the aqueous polysulfide solution made of 1.0 M PMDTA and 0.4 M sulfur at 80 °C provide the thiourea **3a** in 89% yield in 0.5 hour in water (Table 1, entry 1, see ref. [54] and supplementary information for detailed experimental description). Applying sulfur powder with no external base in the reaction of **1a** and **2a** at 80 °C, we only observed traces of the expected thiourea in water (Table 1, entry 2). Applying the mixture



Scheme 2. Multicomponent one-pot synthesis of 2-iminothiazoline **5a**

Table 1. Optimization of the reaction conditions for the synthesis of thioureas starting from aliphatic amines



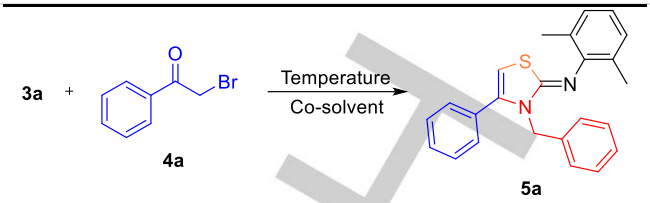
Entry	Temperature [°C]	Co-solvent	Molar excess of **1a** / sulfur atoms / **2a**	Yield[a,b]
1	80	-	1 / 2 / 1.5	89[c]
2	80	-	1 / 1.5 / 1.1	Traces of **3a**
3	**80**	**10% MeCN**	**1 / 1.5 / 1.1**	**>99**
4	80	10% THF	1 / 1.5 / 1.1	90
5	**80**	**10% dioxane**	**1 / 1.5 / 1.1**	**98**
6	80	10% MeCN	1 / 1.3 / 1.1	91
7	80	10% MeCN	1 / 2 / 1.1	97
8[d]	60	10% MeCN	1 / 1.5 / 1.1	81

[a] Reaction conditions: 2,6-dimethylphenyl isocyanide (1a, 0.5 mmol), sulfur, benzylamine (2a), water and co-solvent mixture (2.5 mL), temperature, 0.5 hour; [b] Isolated yields; [c] Applying aqueous polysulfide solution (1.0 M PMDTA/0.4 M S8 in water, 2.5 mL); [d] 1 hour reaction time.

of water:acetonitrile 9:1 in further experiments, the reduction of the excess of sulfur to 1.3 equivalents led to the drop of the yield to 91%, however, raising the excess to 2 equivalents, did not result in better yields (Table 1, entries 6, 7). Performing the reaction at 60 °C led to a longer reaction time providing **3a** in a significantly lower, 81% yield (Table 1, entry 8).

Next, we have performed a brief optimization for the ring annulation leading to 2-iminothiazoline **5a** in the presence of co-solvent. Employing 10% dioxane at 100 °C led to the formation of **5a** in 0.5 hour in 90% yield (Table 2, entry 1). Increasing the temperature to 110 °C did not result in a better yield (Table 2, entry 2). Applying either dioxane or acetonitrile as co-solvent at 80 °C the yield slightly decreased to 87% and 82%, respectively (Table 2, entries 3, 4). Decreasing the excess of 2'-bromoacetophenone to 1.2 equivalent reduced the yield to 85% (Table 2, entry 5). Eventually, we have concluded that the formation of thiourea from benzylamine without an external base requires 80 °C, and 10% co-solvent for the full conversion in 0.5 h. The annulation went smoothly also at 100 °C, and this step suggested dioxane as co-solvent. Using the optimized conditions we have performed the reaction of the isocyanide **1a**, sulfur and benzylamine (**2a**) at 80 °C in a mixture of water:dioxane 9:1 for 0.5 hour, then, sequentially added 2'-bromoacetophenone (**4a**) and continued the reaction at 100 °C for 0.5 hour until the total consumption of the *in situ* generated thiourea followed by HPLC-MS. The hydrogen bromide salt of **5a** precipitated from the reaction mixture, which we isolated by filtration, then washed with 1.0 M aq. NaOH and water providing **5a** in an excellent 91% yield (Scheme 3). Since the process provided the product in higher yield with co-solvents than that in the presence of an external base, we have chosen the former conditions for follow-up. Next, we have evaluated the scope of this multicomponent one-pot

Table 2. Optimization of the reaction conditions for the synthesis of 2-iminothiazolines

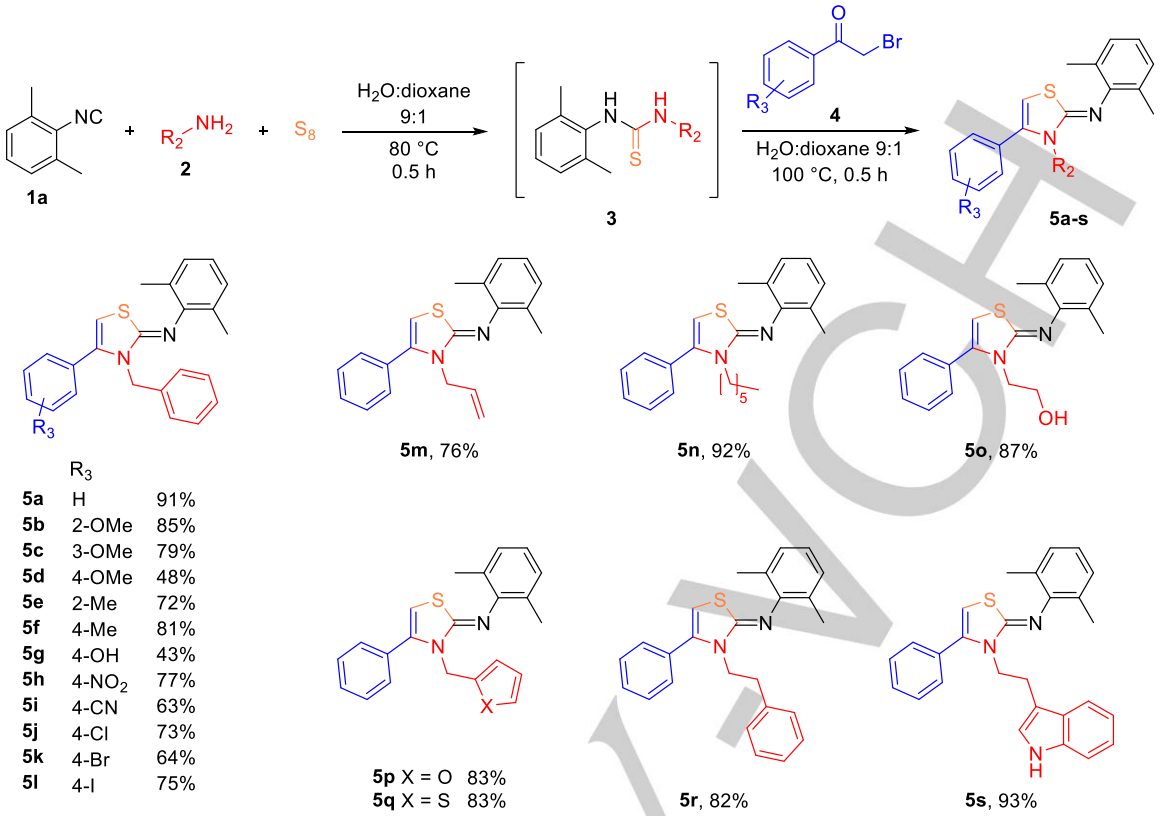


Entry	Temperature [°C]	Co-solvent	Yield[a,b]
1	**100**	**10% dioxane**	**90**
2	110	10% dioxane	89
3	80	10% dioxane	87
4	80	10% MeCN	82
5[c]	100	10% dioxane	85

[a] Reaction conditions: **3a** (0.5 mmol), 2'-bromoacetophenone (**4a**, 0.75 mmol), water and co-solvent mixture (2.5 mL), temperature, 0.5 hour; [b] Isolated yields; [c] 0.6 mmol of **4a** was employed.

reaction using the optimized conditions. Electron rich 2'-bromoacetophenones provided the corresponding 2-iminothiazolines in moderate to good yields (**5b**–**g**, 43–85%). No evident electronic effects influenced the reaction, 2'-bromoacetophenones equipped with electron withdrawing groups provided the corresponding iminothiazolines also in good yields (**5h**–**l**, 63–77%). This reaction setup tolerated nitrile and nitro groups and all of the halogen atoms offering functionalities for further modifications. Next, applying the aliphatic allyl-, hexyl- and ethanolamine, we have obtained 2-iminothiazolines **5m–o** in 76%, 92% and 87% yields, respectively. 2-Aminomethylfurane and 2-aminomethylthiophene both gave the corresponding2-iminothiazolines **5p** and **5q** in 83% yield. 2-Phenetylamine and tryptamine reacted smoothly and selectively leading to the desired heterocycles **5r** and **5s** in excellent 82% and 93% yields, respectively.

The weak nucleophilicity of anilines makes them unable to efficiently cleave sulfur-sulfur covalent bonds and unlike to benzylamine it does not activate sulfur. Therefore, in this case we have applied the aqueous polysulfide solution made from 1.0 M PMDTA and 0.4 M sulfur.[54,56] The reaction of phenethyl isocyanide (**1b**), aniline (**7a**) and the aqueous polysulfide solution made of PMDTA and sulfur at 80 °C was followed by HPLC-MS and after full conversion of the isocyanide, the reaction mixture was acidified with cc. aq. HBr. Then, we added **4a**, and continued the reaction at 100 °C for another 0.5 hour. After full consumption of the thiourea intermediate, we filtered the reaction mixture and washed the product with 1.0 M aq. NaOH that provided the 2-iminothiazoline **5t** in 68% yield (Scheme 4). In contrast to the reaction setup demonstrated in Scheme 2 and 3, here the isocyanide provide the thiourea NH group with higher pK_a value. Eventually, this leads to the regioselective incorporation of the isocyanide in the heterocycle, with the aniline ending up at the 2nd position. Anilines equipped with electron donating groups led to the corresponding iminothiazolines **5u**, **v** and **x** in 52%, 66% and 77% yields respectively. As the 4-OMe derivative **5w** have remained an oil both as a salt and in neutral form, this was isolated after flash chromatography. Applying the anilines equipped with

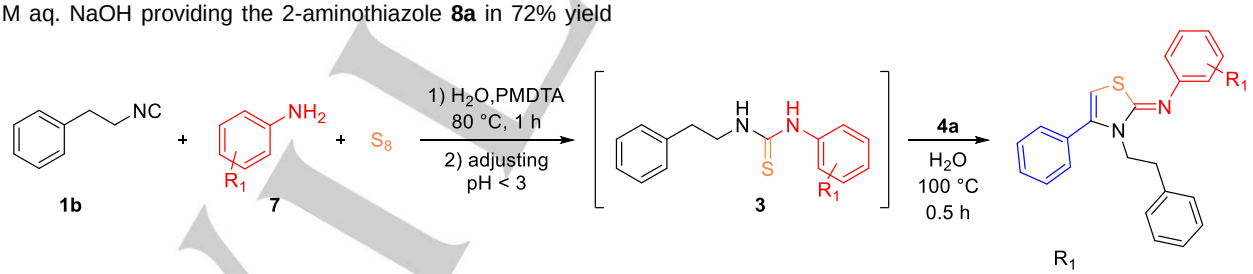


	R_3	
5a	H	91%
5b	2-OMe	85%
5c	3-OMe	79%
5d	4-OMe	48%
5e	2-Me	72%
5f	4-Me	81%
5g	4-OH	43%
5h	4-NO_2	77%
5i	4-CN	63%
5j	4-Cl	73%
5k	4-Br	64%
5l	4-I	75%

Scheme 3. Scope of 2'-bromoacetophenones (**4**) and aliphatic amines (**2**)

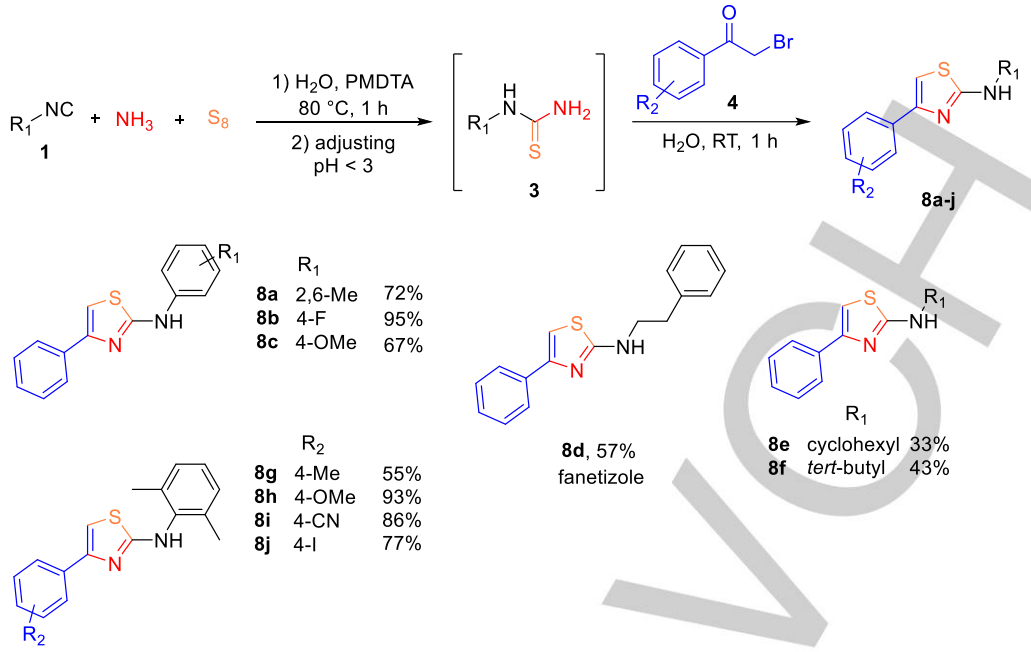
halogen atoms resulted in the formation of the iminothiazolines **5y**–**5za** in good 68–81% yields respectively.

Employing aqueous ammonia, 2,6-dimethylphenyl isocyanide (**1a**) and the polysulfide solution made of PMDTA and sulfur and at 80 °C led to the full conversion of **1a** to the corresponding thiourea **3** in 1 hour. Adjusting the pH of the reaction below pH 3 with cc aq. HBr followed by the addition of 2'-bromoacetophenone (**4a**) resulted in the precipitation of the HBr salt of **8a** after 1 hour at room temperature. After filtration, the product was washed with 1.0 M aq. NaOH providing the 2-aminothiazole **8a** in 72% yield (Scheme 5). 4-Fluorophenyl and 4-methoxyphenyl isocyanides lead to the desired thiazoles **8b** and **8c** in 95% and 67% yield respectively. Phenethyl, cyclohexyl and *tert*-butyl isocyanides gave rise to the corresponding thiazoles **8e**,**f** and the anti-inflammatory fanetizole **8d** in moderate yields.[64] Notably, the salts of **8b**, **8e** and **8f** were oil and therefore these products were purified by flash chromatography. Various 2'-bromoacetophenones underwent the reaction smoothly, providing the thiazoles **8g**–**8j** in moderate to excellent yields (55–93%).



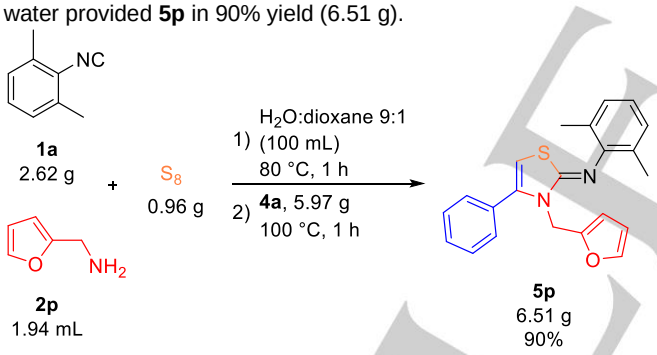
	R_1	
5t	H	68%
5u	2-Me	52%
5v	4-Me	66%
5w	4-OMe	48%
5x	4-OH	77%
5y	4-Cl	81%
5z	4-Br	78%
5za	4-I	68%

Scheme 4. Scope of anilines (**7**)



Scheme 5. Scope of isocyanides (**1**) and 2'-bromoacetophenones (**4**) for the synthesis of thiazoles (**8a–j**)

To demonstrate the robustness of the reaction we performed the 40-fold scale-up synthesis of **5p** (20 mmol, Scheme 6). To our delight, both the preparation of the thiourea and thiazolimine was ready in 1 hour leading to the desired heterocycle. Filtration of the crude product, treatment with 1.0 M aq. NaOH and washing with water provided **5p** in 90% yield (6.51 g).



Scheme 6. Scale-up synthesis of **5p**

Conclusion

In summary, we have developed an aqueous multicomponent one-pot method for the synthesis of a large and diverse set of 2,3,4-trisubstituted 2-iminothiazolines and 2,4-disubstituted 2-aminothiazoles, starting from isocyanides, sulfur or polysulfide solution, aliphatic amines, anilines or ammonia and 2'-bromoacetophenones. Depending on the nucleophilicity of the amines, the reaction could be performed in pure water or with 10% dioxane as co-solvent. This one-pot protocol features excellent atom economy, functional group tolerance and short reaction times. Isolation of the pure products from the aqueous reaction mixture by a simple filtration in most cases, if solids, provide a convenient experimental execution. The method offers an expedient access to library synthesis which we demonstrated on a diversely functionalized set of 37 compounds from those 31 are first synthesized here, and also enables scale-up to multiple grams.

Acknowledgements

Krisztina Németh and Pál Szabó for the HRMS measurements. P. Ábrányi-Balogh was supported by the Hungarian Science Foundation OTKA (PD124598) grant.

Keywords: sulfur • multicomponent reaction • 2-iminothiazoline • 2-aminothiazole • aqueous polysulfide solution

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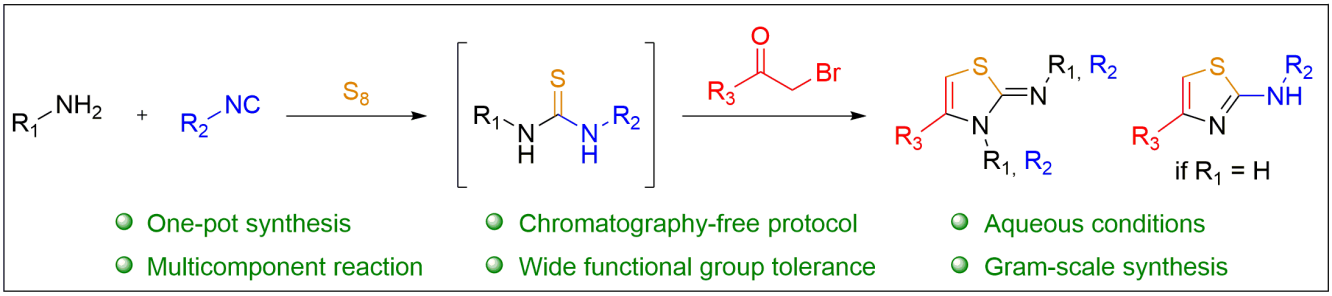

A multicomponent one-pot process led to the formation of diversely trisubstituted 2-iminothiazolines and disubstituted 2-aminothiazoles under aqueous conditions. Starting from isocyanides, amines, 2'-bromoacetophenones and aqueous polysulfide solution or sulfur powder, this efficient procedure enabled the chromatography-free separation of solid products.