Harnessing Diazoketones for the Efficient Synthesis of 2,4-Disubstituted Thiazoles: Scalable and Versatile Approach to Important Heterocyclic Scaffolds

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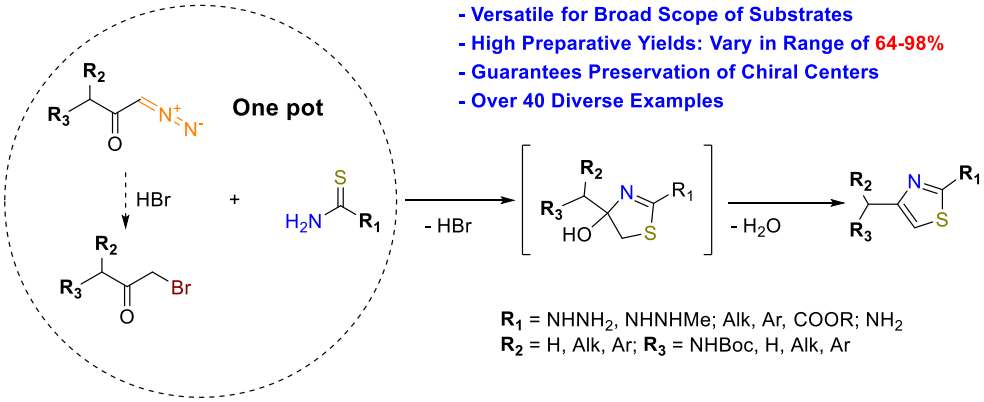


Abstract

This study presents a scalable one-pot synthesis of 2,4-disubstituted-(1,3)thiazoles using diazoketones with thiosemicarbazide or thiourea, achieving high yields across various substrates. Thiazole derivatives demonstrate diverse biological activities (antibacterial, antiviral, anticancer, etc.) and applications in nanoelectronics and material science The suggested approach to their preparation highlights diazoketones as a chemically resilient alternative to traditionally used halogen ketones. This versatile synthesis method expands the scope of available 2,4-disubstituted-(1,3)thiazoles and opens broad opportunities for this class of compounds to contribute to advancements in medicinal chemistry and technology on the next level.

Introduction

Thiazoles, characterized by a five-membered ring containing both sulfur and nitrogen, have garnered significant attention due to their wide range of applications in various fields, which is shown in over 71K publications, specifically 57K journal articles and 14K patents according to SciFinder. Particularly 2,4-disubstituted-(1,3)thiazoles are of interest in medicinal chemistry and material science, demonstrating remarkable versatility and utility. The interest in thiazoles, especially the 2,4-disubstituted variants, stems from their diverse biological activities[1]. These compounds have been extensively studied for their antibacterial properties, effective against various bacterial strains[1-11], and their antiviral activities, including potential efficacy against HIV and other viruses[10, 12-13]. The antiparasitic capabilities of these thiazoles further extend their medicinal relevance, potentially contributing to treatments for parasite-induced diseases[6, 11]. Moreover, the anti-inflammatory[2, 14-16] and anticancer[1, 4, 13, 17-27] properties of 2,4-disubstituted-(1,3)thiazoles have a potential to substantial contribute to the treatment of chronic inflammatory diseases and various types of cancer. Their integration into bioactive peptides has highlighted their potential in drug development, where they contribute to enhanced stability and efficacy of peptide-based bioactive compounds and therapeutics[3-4, 10, 27-35]. Beyond their biomedical applications, these compounds have found roles in nanoelectronics[36-37] and material science[38-41], where their chemical properties contribute to advancements in electronic devices and novel materials.

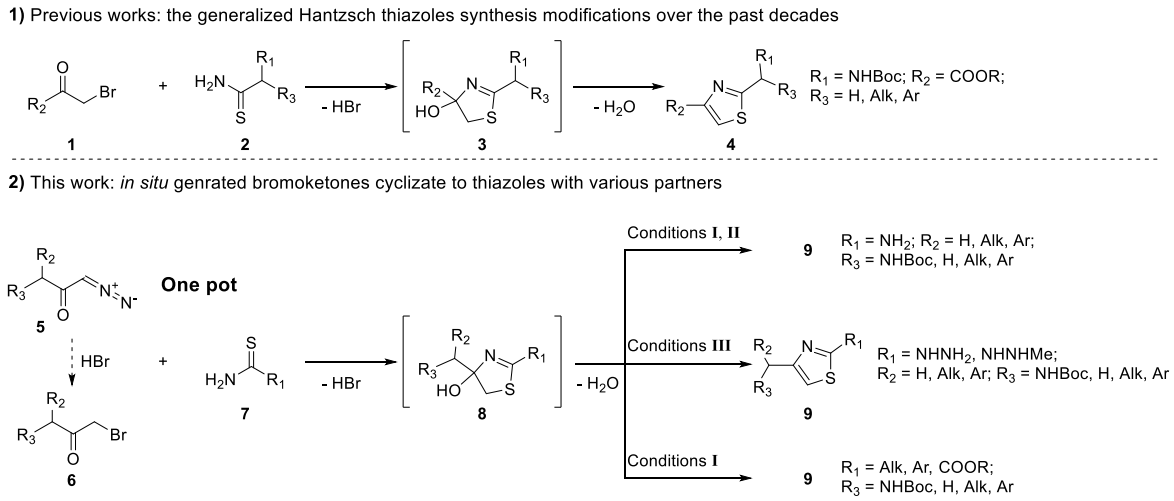
The journey of synthesizing 2,4-disubstituted thiazoles is marked by a progression from classical methods to innovative green chemistry approaches, mirroring the evolution of organic synthesis over decades. The pioneering Hantzsch method, dating back to 1887, laid the groundwork with its use of α-haloketones and thioamides or thioureas for intramolecular cyclization[42]. This method was further expanded by Gabriel's 1910 method[43] and subsequent advancements by Tcherniac (1919)[44] and Cook-Heilbronn (1947)[45], who introduced techniques such as cyclizing dithiocarbazates with α-haloketones. In 1974, Dubs' used new approach, employing mercaptoacetaldehyde dimer in a reaction with ammonia and various aliphatic aldehydes, followed by quinone-induced dehydrogenation[46]. The shift to multicomponent, one-pot

reactions signified a major advancement towards sustainability and efficiency in thiazole synthesis. The choice of solvent, a critical aspect of reaction efficiency and environmental impact, became a focal point, with solvent-mediated reactions gaining prominence[47-53]. Also the recent method for regioselective synthesis of substituted thiazoles from chromone derivatives and thioamides, is worth mentioning in the context[54]. Catalysis in thiazole synthesis has evolved with the use of diverse catalysts, including asparagine functionalized aluminum oxide nanoparticles[55], glycerol/cetrimonium bromide (CTAB) micels[56], gold catalysts enhanced by PN-bidentate ligands[57], ionic liquids[58], Bronsted[59] and Lewis acids[60], along with copper[61], palladium[62]-based catalysts and photocatalytic systems[63]. This have significantly broadened the scope of catalytic approaches to thiazole synthesis. Solid-support synthesis techniques for thiazole preparation, like the conversion of nitriles to thioamides on Rink amide resin[64], and the Tebbe olefination of polymer-supported esters on Merrifield resin via brominated intermediates[65] highlight the versatility and efficiency of solid-support in organic chemistry. Recent trends have steered towards solvent-free methods, emphasizing an environmentally benign approach. Notable among these are one-pot microwave-assisted[66] and grinding methods[67-68] for synthesizing 2,4-disubstituted thiazoles, which eliminate the use of solvents and catalysts, thus contributing to a more sustainable chemistry. Looking back, the synthesis of 2,4-disubstituted thiazoles has witnessed a significant transition from classical methodologies to modern green chemistry approaches, reflecting the field's ongoing commitment to sustainability, efficiency, and innovation. These developments have positioned thiazole production at the vanguard of modern synthetic practices. While these novel methods represent a confluence of efficiency, convenience, and green principles, challenges such as harsh reaction conditions, unsatisfactory yields, and difficult product isolation persist, calling for the development of more efficient protocols.

In our work, we offer a modified method for the synthesis of 2,4-disubstituted-(1,3)thiazoles, utilizing diazoketones for a straightforward one-pot procedure with thiourea and thiosemicarbazide. Diazoketones serve as stable and convenient synthetic equivalents for halogen ketones. This method is a versatile and scalable in-depth rework of classical Hantzsch synthesis[42], underscoring its potential utility in various applications. Our approach not only demonstrates innovation in synthetic chemistry but also aligns with the increasing need for sustainable and efficient chemical processes.

Results and Discussion

The classical Hantzsch thiazole synthesis has undergone numerous improvements and modifications throughout past decades. A key feature which connects the vast majority of such modifications is the introduction of the “halfway” formation of the hydroxythiazoline intermediate **3** (**Scheme 1**, **(1)**) and addition of reagents to activate **3**, facilitating the necessary elimination to furnish thiazole **4** (**Scheme 1**, **1)**). Further studies by Meyers et al. examined the effect of using different reagents and conditions to eliminate the intermediate hydroxythiazoline to form the desired thiazole product[69]. In our modification we used AADDK and other diazoketons, which we previously found to be bench-stable and readily available reagents[70], in presence of HBr, in order to bypass the synthesis and isolation of haloketones, which are known for their instability and lacrimatory effect. This approach allowed us to generate haloketones **6** (**Scheme 1**, **(2)**) *in situ* and react them with thiourea(s), thiosemicarbazide(s) and thioamides **7**, (**Scheme 1**, **(2)**) so that the added HBr, as well as the released during the cyclization stage, catalyzed the dehydration of **8**, (**Scheme 1**, **(2)**).



Scheme 1. 1) Generelized scheme of Hantzsch synthesis in its modern understanding; 2) the modification of Hantzsch synthesis implemented in this work.

Synthesis of amino acid (AA)-derived amino thiazoles is an important part of the thiazole chemistry, because it provides material for thiazole-containing peptides[Ref] and other biologically active compounds[Ref]. This demands

methods suitable to preserve the configuration of the starting AAs. The attempts to adapt the Hantzsch thiazole synthesis for use with substrates prone to racemization led to modification of the standard reaction conditions which led to AA-derived thiazoles in high enantiomeric purity by using a lower reaction temperature and basic reaction conditions[71]. As for a model substrate, we took AADDK based on optically active alanine (see **Table S1** in the SI). This substrate was also used to optimize the solvent type and reagent ratio (**Table S1**, SI). The optimization allowed us to come up with the isopropanol (*i*-PrOH) as the most suitable solvent and the ratio between diazoketone:thiourea:hydrobromic acid as 1:1:1.1. The general procedure included gradually adding (approximately 2 hours) concentrated aqueous HBr solution to a mixture of diazoketone and thiourea in *i*-PrOH at 0°C and after completing the acid addition, heating the reaction mixture at 50 °C during additional 3 hours. Aiming to extend the method to a broader range of substrates and to test its effectiveness with sterically hindered or inherently unstable haloketones, we synthesized a series of diazoketones and performed cyclization following the general procedure above (**Figure 1 A**). Treating the mixture with an additional portion of acid allowed us to remove the protective group and obtain diaminothiazoles as dihydrobromide salts (**Figure 1 B**). Notable, the presence of a substituent on the nitrogen atom of thiourea did not significantly affect the reaction's course, enabling the synthesis of 2-*N*-substituted amitotiazoles.

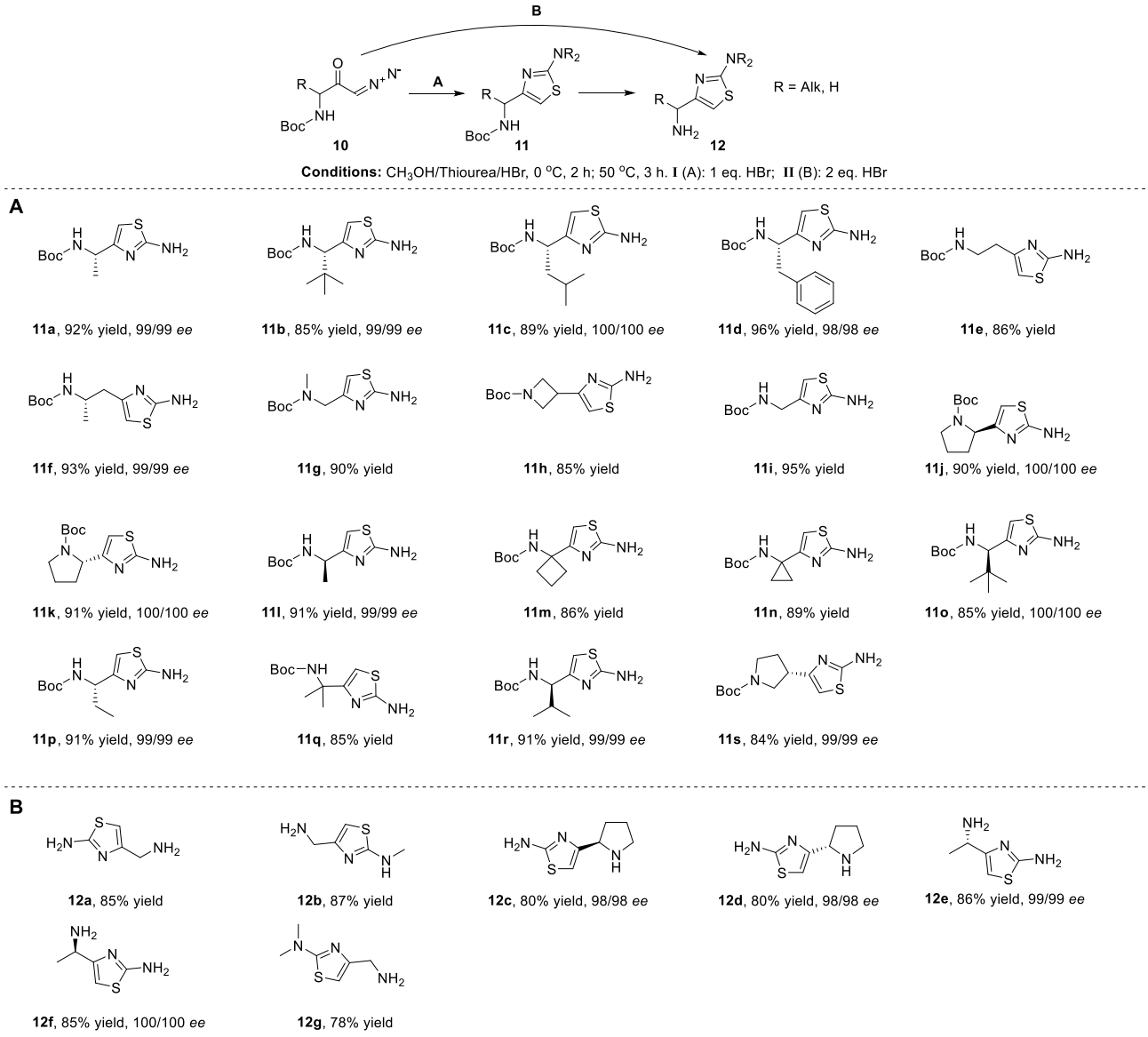


Figure 1. Synthesis of AA-Derived amino thiazoles. **A:** 4-*N*-Boc-aminoalkyl-2-aminotyhiazoles; **B:** De-Bocilated-aminoalkyl-2-aminotyhiazoles

The developed protocols **A** and **B** (**Figure 1**) allowed for the synthesis of desired thiazoles with retaining the *N*-Boc protecting group (**A**), or removing it (**B**), resulting thiazoles hydrobromides as ready to use building blocks. As with

basic systems[71], the enantiomeric purity of the reaction products is maintained. The structure, yields, and scale for the prepared compounds are given in the **Figure 1**.

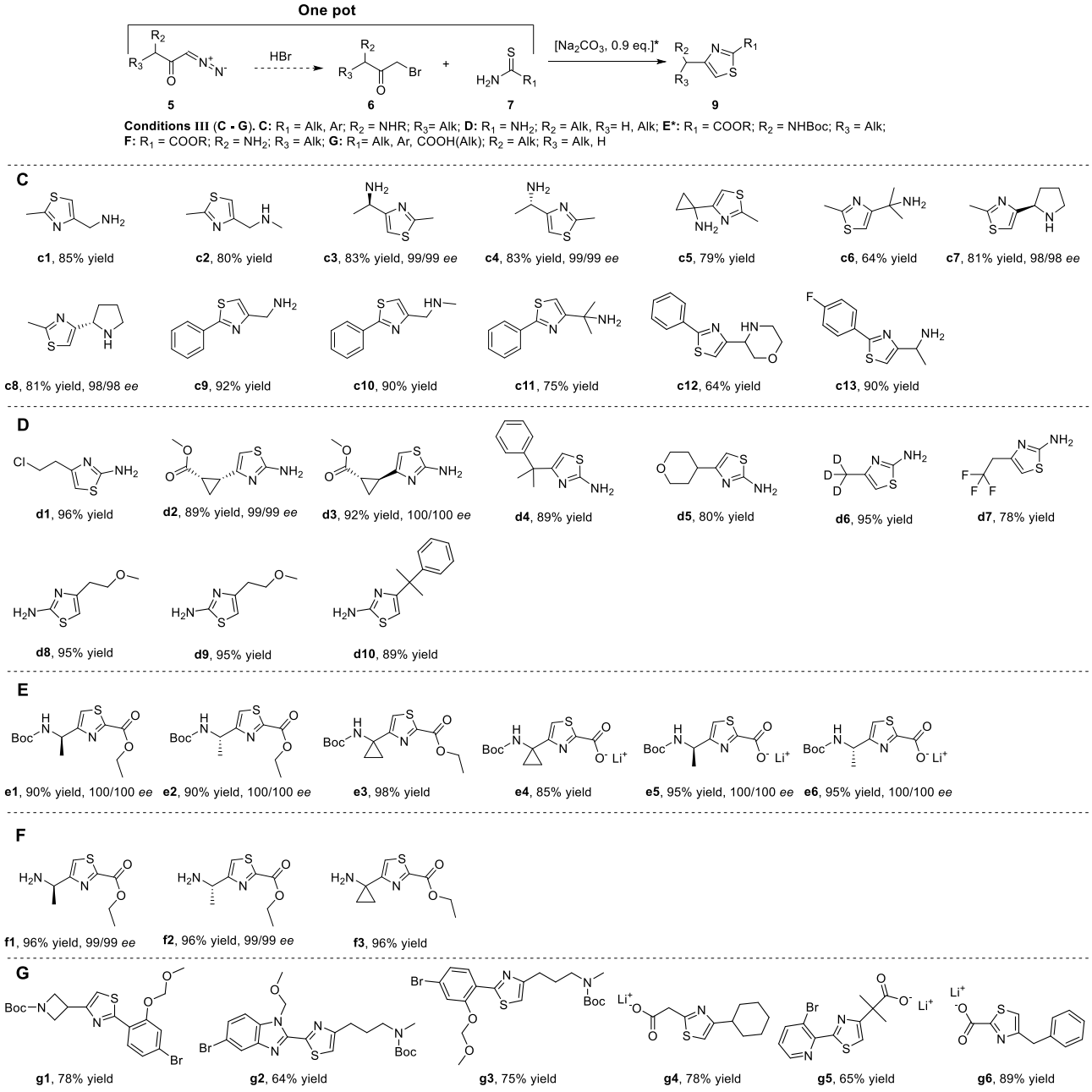
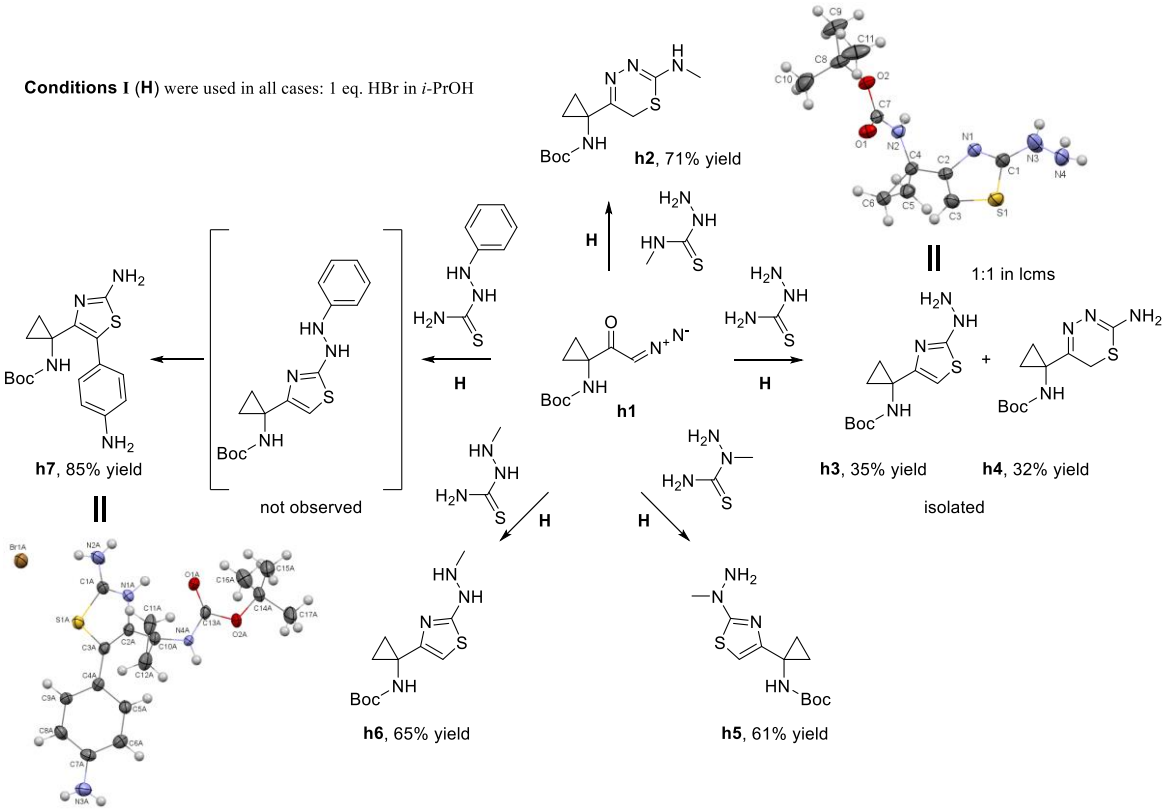


Figure 2. Synthesis of amino thiazoles using the modified Hantzsch protocol with diazoketones: scope and limitations.

Our modification of Hantzsch synthesis, when using both aliphatic and aromatic thioamides wit AADDKs, lead to the formation of a thiazoles with respective hydrocarbon substituent at position 2 with good yields (**Figure 2**, **C**). However, unlike in cases of 2-aminothiazoles above, the HBr formed during the reaction did not bind as strongly, and this allowed to obtain the desired 4-alkylamino thiazoles from corresponding *N*-Boc protected AADDKs directly as hydrobromic salts (**Figure 2**, **C**). The reaction of aliphatic and aromatic diazoketones under standard conditions yielded corresponding thiazoles with high preparative yields. Notable, compounds like 4-(methyl-*d3*)thiazol-2-amine **d6**, whose potentially parent haloketones are prone to deuterium migration, and 4-(2,2,2-trifluoroethyl)thiazol-2-amine **d7** as well as cyclopropane derivatives **d1-3**, which have extremely unstable corresponding haloketones, were successfully synthesized for the first time using our one-pot method from diazoketones with high yields (**Figure 2**, **D**). An interesting challenge was to synthesize thiazoles with an ester group at position 2 of the thiazole core, using ethyl 2-amino-2-thioxoacetate or structurally similar compounds. The standard procedure was inadequate for synthesizing this series of compounds. The reaction product formed as a hydrobromide salt as planned, but yields did not exceed 20-30%, regardless of changes in

reagent ratios, solvents, or temperature conditions. A significant amount of ammonium salt was also isolated alongside the reaction product. This observation led to the conclusion that the HBr formed during the process hydrolyzed the thioamide core in parallel to its formation in the cyclization process, likely due to the acceptor effect of the ester group. The first attempt to circumvent this problem using excess Na_2CO_3 as a base to neutralize the acid, resulted in a mixture of the target product and a hydrate of general formula **8** (**Scheme 1**, **II**) in a 1:3 ratio. Given the well-studied mechanism of the reaction, the formation of the hydrate **8** was not surprising. Isolating this mixture and converting it to a pure dehydrated form was doable but this unnecessarily complicated our protocol. Thus, based on the experimental data collected, more favorable conditions were sought between these two extremes. The solution was found using 0.9 equivalents of base (Na_2CO_3), which happened to be sufficient to bind most of the acid, complicating thioamide hydrolysis and removal of acid-sensitive protective groups (Boc), but still adequate for catalyzing the **8** dehydrations. Using this enhanced procedure, we successfully synthesized a number of *N*-Boc-protected aminoester thiazoles **e1**-**3** (**Figure 2**, **E**). Although we were unable to deprotect **e1**-**3** directly in the reaction environment, the use of standard HCl solution in dioxane in CH_2Cl_2 media allowed the smooth de-Bocilation without degrading the thiazole core (**Figure 2**, **F**). Ether hydrolysis on the other side resulted **e4**-**6** as lithium salts (**Figure 2**, **E**). Additionally, our research explored the direct synthesis of large molecular weight scaffolds with more complex structures, potentially attractive for medicinal chemistry, including lithium salts of 2-thiazoloacetic and 2-thiazolecarboxylic acids, which are typically challenging to isolate and store due to the 2-thiazolic acids' tendency to easily decarboxylate.



Scheme 2. Reactions of AADDK **h1** with various thiosemicarbazides and XRD structures of prodeucts **h7** and **h3**.

Condensation of thiosemicarbazide (TSC) with α-halogencarbonyl compounds can lead to the formation of three isomeric products: 2-amino-6*H*-1,3,4-thiadiazines, 2-hydrazinothiazoles, and 3-amino-2-thiazolinimines[72]. When this reaction is carried out in ethanol, thiadiazines form with low yields due to the isomers mixture formation. Literature dedicated to studying the conditions for 1,3,4-thiadiazine formation yet not give clear explanations to the chemistry behind it and the ratios of the isomers forming in such reactions[73]. In this study, we examined the condensation products of thiosemicarbazide with AADDK under previously described reaction **Conditions I** (**Scheme 2**). The *in situ* generated α-halogenketones reacted with TSC upon boiling in *i*-PrOH, affording mixtures of 2-hydrazinothiazole **h3** (major) and a 5-substituted derivative of 2-amino-6*H*-1,3,4-thiadiazine (**h4**). Under these conditions, a mixture of two compounds was formed in a ratio close to 1:1. These products were separated and characterized. The structure of hydrazine was confirmed using XRD (**Scheme 2**, **h3**). The 1,3,4-thiadiazine system matched ^{1}H NMR data with previously characterized aryl-substituted 1,3,4-thiadiazines, synthesized using more accessible bromoacetophenones[74].It is particularly noteworthy that deeper investigation of the process, especially the dependence of the product ratio on the nature of the solvent and the pH

of the environment, can be of significant interest both fundamentally and practically, and needs additional in-depth study. Meantime in the given conditions (**Conditions I**), the reaction was directed towards the formation of one possible isomer or another quantitatively with close preparative yields (see **Scheme 2**, **h5** and **h6**), depending on the regio-position of the methyl in the hydrazine group of the respective methyl-substituted thiosemicarbazides. For instance, the presence of a substituent on the "hydrazine side" denies the possibility of formation of **h2**-type 1,3,4-thiadiazines. In cases when the methyl substituent sited on the "amine side", the formation of the hydrazine was not observed, and the only reaction product found was the derivative of 1,3,4-thiadiazine (**Scheme 2**, **h2**). Based on these examples, it can be concluded that the course of the cyclization reactions of AADDKs with thiosemicarbazides can be controlled via inactivating certain sites in these thiosemicarbazides by introducing alkyl substituents and/or protective groups in the hydrazine fragments. If phenyl-substituted thiosemicarbazide was used, the intermediate formed immediately underwent Benzidine rearrangement under given reaction conditions, resulting derivative **h7**, as it is shown in **Scheme 2**. The structure of **h7** was additionally investigated using XRD analysis (**Scheme 2**).

Conclusions

In our study, we have successfully developed a scalable and efficient one-pot synthesis method for 2,4-disubstituted-(1,3)thiazoles by reacting AADDKs with diazoketones, thioureas, thioamides, and thiosemicarbazides. This approach has proven to be a significant improvement over traditional halogen ketone-based methods, allowing for high-yield production of a diverse array of thiazoles. Central to our innovation is the use of diazoketones, particularly AADDKs, which has been instrumental in maintaining the enantiomeric purity, providing higher yields and scales, as well as significant broadening the scope of the synthesized thiazoles. The optimized reaction conditions allowed us to extend this method to a broader range of substrates, including the steric hindered ones or compounds previously unavailable due to inherent instability.of parent halogen ketones. Our findings make a substantial contribution to the field of synthetic chemistry, aligning with the current trends towards sustainable and efficient chemical processes. In summary, our work represents a significant step forward in the synthesis of 2,4-disubstituted-(1,3)thiazoles, showcasing the dynamic and adaptable nature of modern synthetic chemistry. By addressing key challenges in thiazole synthesis, we pave the way for further advancements in both synthesis and applications for this remarkable class of compounds, already proven exceptionally valuable in drug discovery, agrochemistry and material science.

Experimental Section

General information and materials: The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on automated melting point system. 1H, 13C, and NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Tetramethylsilane (1H, 13C) were used as standards. HPLC analyses were done on an Agilent 1200. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). X-Ray crystallography was measured on Bruker Smart Apex II diffractometer. Column chromatography was performed with silica gel (200-300 mesh).

General Procedure (Conditions I): Dissolve AADDK and 1.2 eq of the thiourea/thioamide or thiosemicarbazide (complete dissolution of the latter is not necessary) in *i*-PrOH. Add 2.5 eq HBr conc. (strong release of nitrogen better to add it drop by drop). Slightly exothermic reaction is observed, but it's not in critical or danger zone. After approximately three hours of heating, (depending on the pair of substrates), a precipitate of the final product (as HBr salt) may form. Regardless of the substrate, up to 20% of the substance remains in solution, so evaporation of the reaction mixture is recommended. On the next step $NaHCO_3$ solution workup can be performed, followed by EtOAc extraction and chromatographical purification. In many cases HBr salt can be purified by washing it with several portions of MTBE. (in this case some NH_4Cl from thioamide hydrolysis can be found as an impurity).

Recommended concentrations of AADDK < 0.2M. Recommended reaction mass volume for 8 ml vial: not more than 5 ml (1 mmol of substrate in 5 ml of solvent). HBr should be used without dilution. *i*-PrOH can be switched for other alcohols (however it should be noted that its boiling point was found optimal for the most of the cases). It is possible that for some sterically hindered substrates higher reaction temperatures or longer reaction times would be needed.

Conditions II: Same as for **Conditions I**, but 1.5 eq HBr used: when diazoketone does not contain of *N*-Boc protecting group, or it is acceptable/needed to remove it, average workup is performed with 1.5 eq HBr provide same result in thioamide/thioureas cases. Importantly, acid/base purification cannot be used in case of neutral thioamides due to the low pKb of thiazole ring.

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