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COMMUNICATION

Four-component thiazole formation from simple chemicals under metal-free conditions

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Jingjing Jiang, Huawen Huang,* and Guo-Jun Deng*

Multi-component reactions for the synthesis of polysubstituted thiazoles from simple chemicals are described. Under metal-free reaction conditions cheap and easily available ketones, aldehydes, ammonium salt, and elemental sulfur are self-assembled to provide entries to three thiazoles in moderate to good yield with a range of functionalities tolerated.

The one-pot consecutive multi-component assembly is an important principle in nature for the construction of bonds in the biosynthesis of numerous natural products with the assistance of enzymes. Due to the featured productivity, yield, convergence and facile execution, it is also considered as a powerful strategy to the preparation of valuable compounds in molecular synthesis.[1] Thus the design and discovery of novel multi-component reactions (MCR) have been drawing intensive interests from synthetic chemistry.[1-2]

Thiazole is an important five-membered heterocycle, which as a key unit widely exists in pharmaceuticals,[3] naturally occurring products,[4] and functional materials.[5] The versatile bio-activities of thiazole compounds in metabolism have triggered considerable efforts on the structural and synthetic development. While cyclization between highly functionalized α-bromoketones and thioamides under base conditions is considered as the most common method to construct thiazole ring,[6] noble-metal-catalyzed sequentially stepwise thiazole C–H functionalization provides an alternative entry to multi-substituted thiazoles (Figure 1, a).[7] Regarding multi-component reactions for the construction of thiazoles, in 2015, Miura *et al.* reported a sequential procedure for the synthesis of 2,5-disubstituted thiazoles from terminal alkynes, sulfonyl azides, and thionoesters, in which copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes with sulfonyl azides followed by rhodium(II)-catalyzed coupling with thionoesters and deprotective aromatization.[8] In 2018, Guo and co-workers have developed base-promoted metal-/oxidant-free three-component tandem annulations the construction of 2,4,5 - trisubstituted thiazoles via C−N bond cleavage of amidines.[9] While benzothiazoles have been intensively constructed with cheap and bench-stable elemental sulfur,[10] thiazole formation is rare. In 2018, Yan *et al.* reported an iron-catalyzed atom economical approach for the synthesis of substituted thiazoles starting from enamines and elemental sulfur through the C-H functionalization/C-S bond formation (Figure 1, b).[11] And Jiao group has recently disclosed a copper-catalyzed aerobic three-

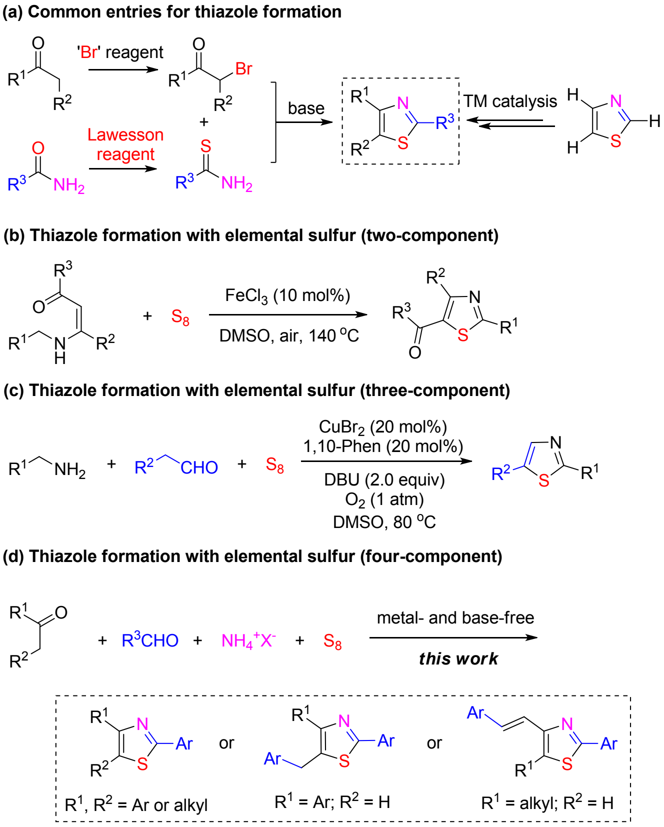

Figure 1. Methods for thiazole formation. (TM = transition metal)

Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China; Fax: (+86)0731-5829-2251; Tel: (+86)0731-5829-8601; E-mail: hwhuang@xtu.edu.cn, gjdeng@xtu.edu.cn

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x component annulation for the synthesis of 2,5-disubstituted thiazoles (Figure 1, c).[12] In spite of these proven utilities, the synthetic development of a more straightforward route from simple chemicals to trisubstituted thiazoles remains highly desirable. Herein, we have now revealed a four-component reaction which obviates the needs of prefunctionalized starting materials and metal catalysts (Figure 1, d). By this protocol, the concise formation of three trisubstituted thiazoles is selectively realized through the condensation with different ketones. Hence, the reactions with methyl ketones afford benzyl and vinyl thiazoles via sequentially five-molecular assembly.

Initially, the one-pot condensation reaction of acetophenone (**1a**), benzaldehyde (**2a**), ammonium iodide, and elemental sulfur in pyridine revealed a five-molecular assembly to afford 2,4-diphenyl-5-benzylthiazole (**3a**), even with equally stoichiometric amounts of **1a** and **2a** (Figure 2, path a). The kinetic studies on this transformation indicated that the dehydrative Aldol condensation of **1a** and **2a** to form chalcone **A** occurred very fast (complete within 10 min), which therefore prohibited the interaction of **1a**, ammonium, and sulfur (Willgerodt reaction). In the optimization of reaction conditions (See ESI for details), pyridine as the reaction media dramatically enhanced the yield. In this regard, pyridine probably served as a Michael donor to facilitate the nucleophilic attack of **A** to sulfur, thus leading to the formation of the pyridinium intermediate **B**. Besides, the solubilities of inorganic ammonium iodide and elemental sulfur were improved by the addition of water, which thereby led to a further yield enhancement. On the other hand, in the same pyridine/H_2O system the treatment of propiophenone (**1q**) with **2a**, ammonium iodide, and elemental sulfur afforded the expected trisubstituted thiazole **4a** in a moderate yield. Mechanistically, this oxidative annulation probably proceeds through the intermediates **D-G** and involves a key Willgerodt-type sulfuration (Figure 2, path b).

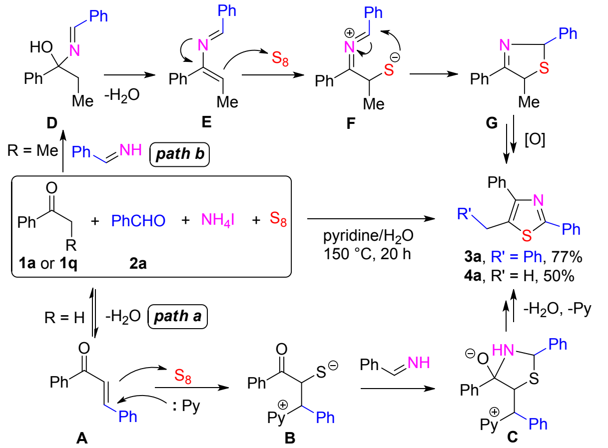

Figure 2. Formation of thiazoles by four-component reactions.

Given the tentative proposal of reaction mechanism based on condensation, we were intrigued by revealing the hydrogen absorption process at the C5 benzylic position of **3a**. Regarding the proposed intermediate **C**, the isotope labeling experiments with deuterated acetophonone (**1a-d$_8$**) and deuterated benzaldehyde (**2a-d$_1$**) excluded the intramolecular hydrogen 1,2- and 1,5-migration, respectively. The result with the addition of deuterium oxide instead of water also supported an intermolecular protonation in the final transformation (Figure 3).

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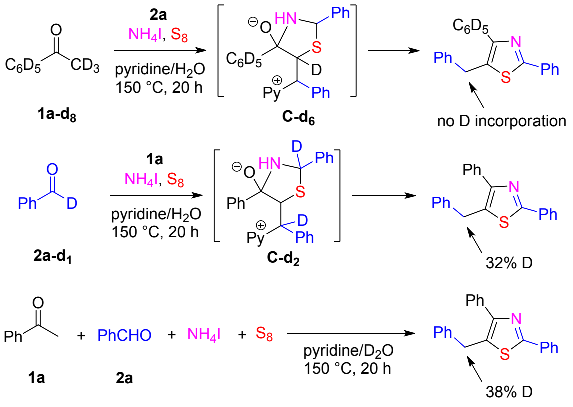

Figure 3. Isotope labeling experiments.

The attempts on the sequential five-component reaction with two different aldehydes were failed either in one-pot or by a two-step operation due to the fast reversible Aldol reaction in present system. In this regard, four substituted thiazoles were generally generated with poor chemoselectivity (Figure 4). We also found that it was ammonium iodide that led to a fast retro Aldol reaction/benzaldehyde exchange.

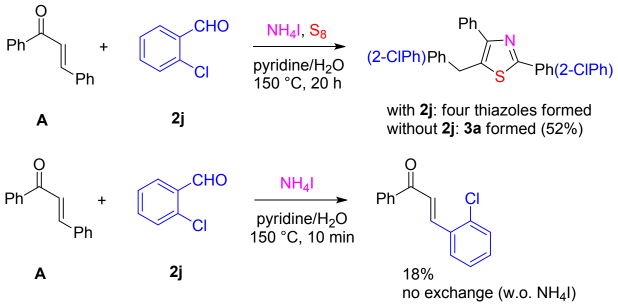

Figure 4. Thiazole formation from chalcone.

With the optimized pyridine/H_2O reaction system in hand, the substrate scope of the four-component thiazole formation was explored (Figure 5). First, methyl aromatic ketones such as substituted acetophenones reacted smoothly to give 5-benzylthiazoles **3a-3m** in moderate to good yields with a broad tolerance of functionalities such as alkyl, alkoxy, halo (F, Cl, Br), and even alkynyl (**3i**). Among them, the substrates bearing electron-donating groups including methoxy afforded the corresponding thiazole in a relatively lower yield (**3g**). Besides, *ortho*-methylacetophenone (**3m**) showed much lower reactivity than its *meta*- and *para*-isomers, featuring an obvious steric hindrance effect. The naphthyl variant was also accommodated to give **3n** in 70% yield. Then, heteroaromatic ketones with thiophenyl and furanyl motifs furnished **3o** and **3p**, respectively, in modest yields. The robust nature of the present five-molecular system was further reflected by the effective gram-scale preparation, in which, for example, **3a** was isolated in 65% yield.

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Subsequently, the generality and limitation of aldehyde components was studied. Notably, in all cases only aromatic aldehydes were productive in present stage, while aliphatic aldehydes generally resulted in an elusive complex mixture. Regarding to substituted benzaldehydes, the desired products were smoothly obtained with yields ranging from 40% to 84% (**3q-3ac**). Among them, halo functionalities (F, Cl, Br) attached at the benzene ring were well tolerated (**3t-3v**, **3y-3z**, and **3ab-3ac**). Interestingly, the configuration of an *ortho*-substituent could improve the reactivity of benzaldehydes, probably due to an effect of neighbouring group participation. For example, 2-chloro- and 2-bromobenzaldehyde featured obviously higher efficiency than their 4- and 3-substituted isomers (**3y** versus **3u** and **3ab**; **3z** versus **3v** and **3ac**). Then, thiophene carbaldehydes were accommodated to afford twofold thiophen-decorated thiazoles **3ad** and **3ae**, albeit in moderate yields. Finally, the bulky 2-naphthaldehyde gave the corresponding product **3af** in 75% yield.

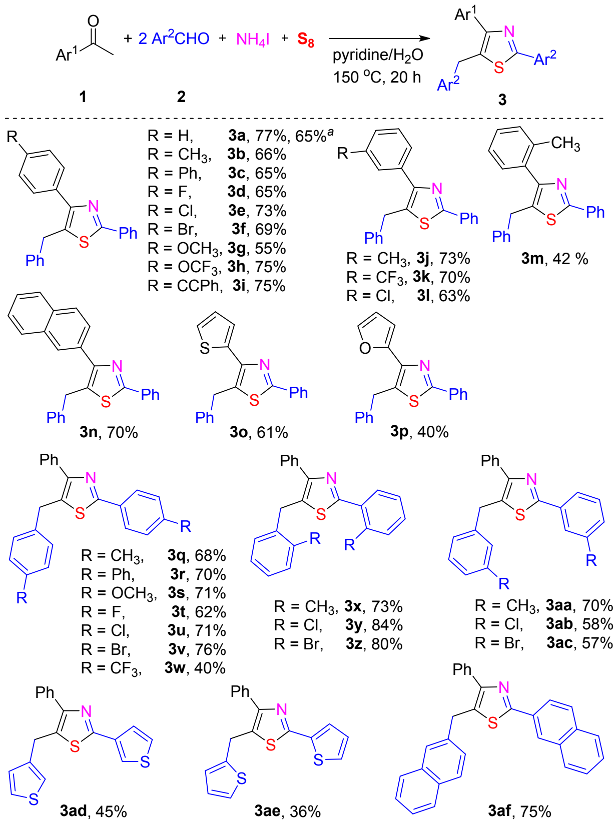

Figure 5. Five-molecular formation of 2,4-diaryl-5-benzylthiazoles. ^{a} Yield of five mmol scale reaction.

As shown above, non-methyl ketones gave formal tetra-substituted thiazoles. The scope of this thiazole formation was then studied (Figure 6). Generally, moderate yields were observed with propiophenone (**4a**), 1,2-diphenylethanone (**4b**), heptan-4-one (**4c**), and some cyclic ketones (**4d-4g**). Notably, the condensation annulation of 4-methoxybenzaldehyde and cyclooctanone afforded the corresponding product **4h** in 80% yield. Synthetically useful functionalities attached to benzaldehydes such as halo (Cl and Br) were acommodated with the present system (**4i-4j**).

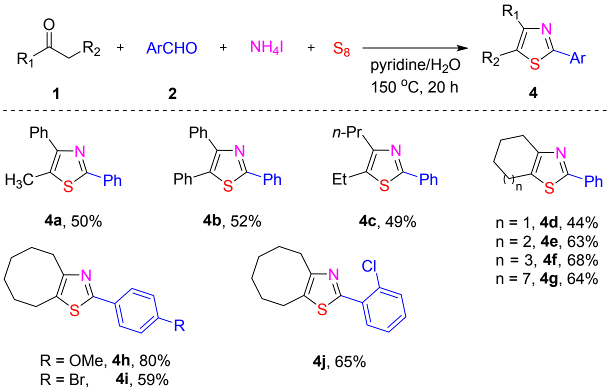

Figure 6. Four-molecular formation of trisubstituted thiazoles.

To our delight, when we subjected aliphatic methylketones to the pyridine system, 4-vinylthiazoles were furnished as the main product. In complementary to the results of above two thiazole formation, this reaction represents another sequential five-molecular assembly. The present observation also revealed in the sulfuration process the methylene adjacent to carbonyl groups was inherently higher reactive upon vinyl groups. Thus the unique reactive selectivity led to a new entry to structurally significant vinylthiazoles that cannot be easily obtained by known synthetic methods. In the modification of reaction conditions (See ESI for details), the addition of BzOH facilitated this thiazole formation. Thereafter, this reaction found to smoothly tolerate a range of aliphatic methylketones and aromatic aldehydes, giving 4-vinylthiazoles **5a-5l** in generally moderate yields (Figure 7).

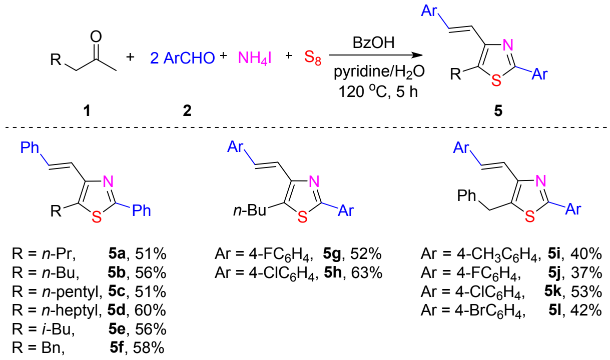

Figure 7. Synthesis of 4-vinylthiazoles from methyl aliphatic ketones.

To further explore the utility and versatility of the present thiazole formation, the late-stage oxidation of the resultant 5-benzylthiazoles was performed (Figure 8). In a modified CuI/TBHP system, while **3a** was oxidized into **6a** with good yield, excellent levels of chemoselectivity was observed when 4-vinyl-5-benzylthiazole **5f** was subjected to this system. Thus, the present protocol provides a stepwise method for 5-benzoylthiazole construction.

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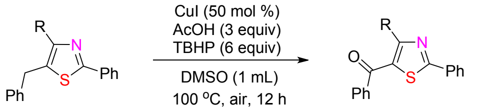

3a, R = Ph
5f, R = styryl

6a, R = Ph, 73%
6b, R = styryl, 53%

Figure 8. Benzylic oxidation of 5-benzylthiazoles.

Conclusions

In summary, we have developed a modular multi-component system for the effective synthesis of 2,4,5-trisubstituted thiazoles by the combination of Debus-Radziszewski imidazole synthesis and Gewald thiophene formation. This metal-free assembly of thiazoles has been oriented by the use of different ketone substrates, i.e. aromatic methylketones, aliphatic methylketones, and non-methylketones. Thus, three substituent-varied thiazoles were afforded with a broad substrate scope. This multi-component protocol that was inspired by classic name reactions represents one of significant progress on reaction discovery with the combinatorial strategy.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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