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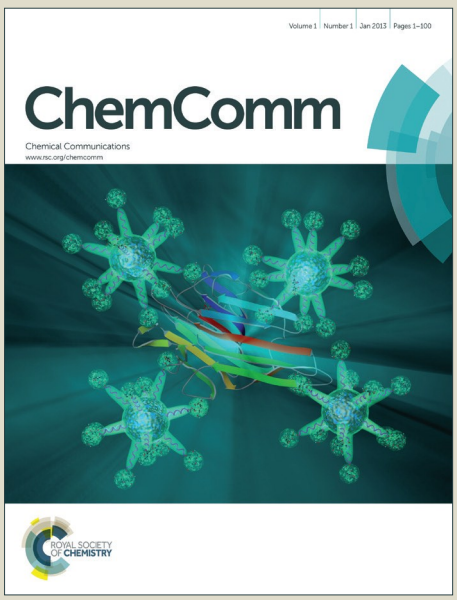

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Diversified Syntheses of Multifunctionalized Thiazole Derivatives via Regioselective and Programmed C-H Activation†

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Accomplished is a sequential construction of diversified multifunctionalized thiazole derivatives through Pd-catalyzed regioselective C-H alkenylation. This versatile approach provides the diversified thiazole derivatives featuring orthogonal substitution patterns at C-2, C-4 and C-5 positions from mono-substituted (2- or 4- substituted) thiazole derivatives or even more challenging simple thiazole.

Introduction

Thiazole-containing molecules represent an important class of structurally privileged heterocyclic compounds that are frequently found in naturally occurring compounds, bioactive entities, pharmaceuticals, as well as functional organic materials.[1] 5-Alkenylated thiazole derivatives and its hydrogenated congeners are of particular interest. For example, 5-alkyl thiazole B was found to be a good agonist of peroxisome proliferator activated receptors (PPARs), which comprise a large family of ligand-activated transcription factors that play a key role in lipid homeostasis (Figure 1).[2] Noteworthy is that only a limited array of such derivatives were investigated due to their unavailability. In view of the importance of such structural motifs, exploration of more active candidates of the thiazole-containing derivatives could be a longstanding goal for the medicinal scientists. Because of this, we herein report the development of a palladium-catalyzed regioselective and stereoselective 5-alkenylation of thiazole derivatives, including 2-substituted, 4-substituted thiazole derivatives, and even more challenging simple thiazole, and application of this established method to the diversified syntheses of multifunctionalized thiazole derivatives.

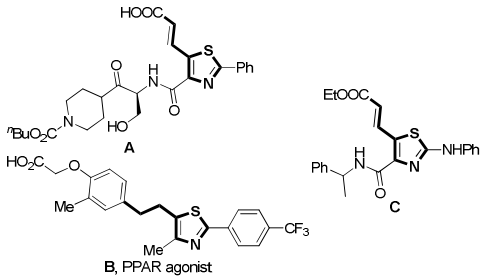

Figure 1 Representatives of the 5-Alkenylated Thiazole Derivatives and its Hydrogenated Congeners.

Recently, direct C-H bond activation/transformation has emerged as a powerful synthetic tool, which has been thus applied to the syntheses of many biologically active natural products as well as pharmaceuticals as a critical step. As an elegant strategy, the synthesis involving C-H activation has emerged owing to the overwhelming merits of the avoidance of prefunctionalization of starting materials and the requirements of atom-economy and step-economy, as well as the ubiquity of C-H bonds in various organic chemicals.[3] Compared with the well documented directed C-H bond activation/transformation,[3c, 4] non-directed C-H bond activation /transformation is less developed.[5] Specifically, the regioselective C-H bond activation/transformation with respect to the well-known important heterocyclic compounds is much less developed.[6, 7i] More importantly, target-oriented development of a method involving the regioselective C-H bond activation of selected molecular scaffolds could be more efficient and feasible for the rapid establishment of a compound library, and consequently, facilitate the search for new drug candidates.[8]

As for the direct C-H activation/functionalization of thiazole derivatives, a series of reaction types have been well developed during the past decade.[6n, 7] Among these, direct alkenylation of thiazole derivatives has been sporadically reported.[9] It is not surprising that the direct oxidative cross-coupling of thiazole derivatives with alkenes is recognized as the most atom-economical approach to the syntheses of alkenylated thiazole derivatives. However, this is a rather challenging transformation since homo-coupling of thiazole derivatives is strongly preferred under oxidative conditions.[10] Notably, 2-alkenylated products were generally obtained when 2-unsubstituted thiazole derivatives were utilized as substrates.[9a] Conversely, to achieve the 5-alkenylation of thiazole derivatives, 2-substituted or even 2,4-disubstituted thiazole derivatives were employed as substrates accordingly.[9c] To date, no report has brought direct regioselective 5-alkenylation reaction to practice with the use of 2,5-unsubstituted thiazole derivatives or even thiazole as substrate.

Results and Discussion

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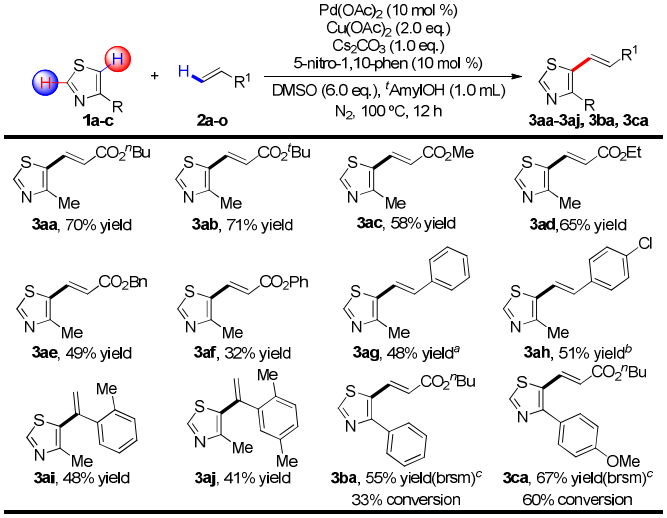
To substantiate the feasibility of direct alkenylation of thiazole derivatives in a regioselective manner, 4-methylthiazole (**1a**) and *n*-butyl acrylate (**2a**) were initially tested as the model substrates. We first embarked on the examination of different solvents by using 10 mol % of $Pd(OAc)_2$ as the catalyst, 2.0 equiv of $Cu(OAc)_2$ as the oxidant and 1.0 equiv of Cs_2CO_3 as the base at 100 °C under N_2 atmosphere (see the supporting information, Table S1). To our delight, with the use of ^{t}AmylOH as the solvent, the reaction proceeded and afforded the desired product in 18% GC yield with the desired regioselectivity, whereas other solvents either gave inferior yields or delivered no product. The structure of desired product **3ac** was further confirmed by comparing to the reported structures. [9a]

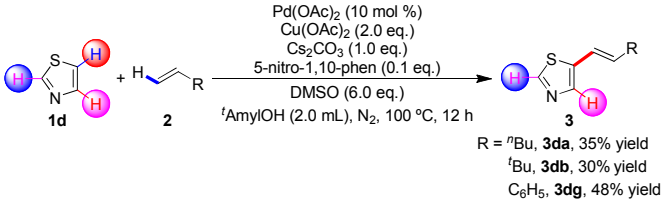
Next, we tested a series of ligands, such as phosphine ligand (**L1**) and *N*-containing ligands (**L2**, **L3**, **L4** and **L5**), and found that the electron-deficient 5-nitro-1,10-phenantroline (**L5**) exhibited the best performance, promoting the reaction to afford the regioselective and stereoselective alkenylated *E*-product (**3aa**) in 51% GC yield (Table S1, entry 9).[11] Moreover, several representative Pd(II) species have been screened. Only cationic palladium species, such as $Pd(OTFA)_2$ and $Pd(CH_3CN)_4(BF_4)_2$ could catalyze the reaction with comparable efficacy in 47% and 48% GC yields, respectively (Table S1, entries 11 and 12). Furthermore, we tried to improve the efficiency by screening various bases and oxidants, but in vain (Table S1, entries 12-16). Finally, further improvement of the efficiency was achieved (70% GC yield, Table S1, entry 17) by introducing 6.0 equiv of DMSO as an additive, of which the coordinative capability might play a crucial role.[12] Moreover, a satisfying isolated yield of 70% could be achieved by using a semi-continuous process by feeding thiazole derivative in five portions (Table S1, entry 18). Thus we established the optimized reaction parameters as following (see the Supporting Information, Table S1): thiazole **1a** (0.2 mmol, in five portions), alkene **2a** (0.5 mmol), 5-nitro-1,10-phenanthroline (0.02 mmol), $Cu(OAc)_2$ (2.0 equiv), Cs_2CO_3 (1.0 equiv), DMSO (6.0 equiv), ^{t}AmylOH (1.0 mL), 100 °C, 12 h.

With the optimized conditions in hand, we immediately examined the scope of different alkene partners. As is shown in Scheme 1, *n*-butyl and *tert*-butyl acrylates smoothly reacted with 4-methylthiazole, affording the desired regioselective and stereoselective alkenylated *E*-products in 70% and 71% yields, respectively. As for the methyl and ethyl acrylates, moderate to good yields (**3ac**, 58% and **3ad**, 65% yields, respectively) were also obtained. Moreover, benzyl acrylate could also be utilized as a qualified partner in this catalytic system to deliver the desired alkenylated *E*-product **3ae** in 49% yield. Noteworthy, phenyl acrylate (**2f**) could also be employed as substrate, although, relatively lower yield of **3af** (32%) was obtained. Interestingly, styrene derivatives could also be well applied to the reaction system and afforded the 4-methyl-5-styrylthiazole derivatives (**3ag-3aj**) in moderate to good yields. It should be noted that when styrene and 4-chlorostyrene were employed as reaction partners, not only the separable *E*-configured internal alkene stereoisomer (**3ag** and **3ah**) could be obtained, but also an inseparable mixture of *Z*-configured internal alkene stereoisomer and terminal alkene product (**3ag'** and **3ag''**, **3ah'** and **3ah''**) were formed as minor product. However, when sterically hindered 2-methylstyrene and 2,5-dimethylstyrene were utilized as substrates, terminal alkene products (**3ai** and **3aj**) were formed as the major products. Besides the 4-methylthiazole, 4-arylthiazole derivatives could also be employed as the substrates, affording the corresponding regioselective 5-alkenyl-4-aryl disubstituted thiazole derivatives (**3ba** and **3ca**) in moderate to good yields (55% and 67%, respectively). This method provided a complementary but straightforward approach to the medicinally important stilbene analogues.



Scheme 1 Scope for the Alkene Partners and 4-Substituted Thiazole Derivatives. Note: [a] Additional inseparable mixture of terminal alkene product (**3ag'**) and *Z*-configured product (**3ag''**) was formed in 24% combined yield (the ratio of **3ag'**/**3ag''** = 10/1). [b] Additional inseparable mixture of terminal alkene product (**3ah'**) and *Z*-configured product (**3ah''**) was formed in 22% combined yield (the ratio of **3ah'**/**3ah''** = 5/1). [c] The reaction was carried out in one pot procedure.

We then turned our attention to examine more challenging thiazole in the direct regioselective and stereoselective alkenylation reaction. As expected, thiazole could also be smoothly coupled with acrylates to deliver the regioselective 5-alkenylated *E*-products in synthetically useful yields when the reactions were carried out in 2.0 mL of ^{t}AmylOH.



Scheme 2 Regioselective and stereoselective Alkenylation of a Challenging Thiazole.

To expand the substrate scope further, we then examined the 2-substituted thiazole derivatives (Scheme 3). Gratifyingly, all 2-arylthiazole derivatives, regardless of the electronic nature on the 2-phenyl group, could be totally tolerated under the established conditions, affording the desired *E*-5-alkenylated 2-arylthiazole derivatives in moderate to good yields (22-88% yields, Scheme 3). Especially, 2-phenylthiazoles bearing a sterically hindered group, such as 2'-methyl and 2'-methoxy groups, have no obvious effect on the reactions and such reactions could proceed quite well, which afforded the desired products in 75% and 77% yields, respectively. Interestingly, an ester group was also compatible, giving the transformable product (**3qa**) in 46% yield. What's more, the strongly coordinating cyano (**3ra**) group, was well tolerated under the optimal conditions, although, relatively lower yield was obtained (39%). Most importantly, the regiochemistry of this method has been unambiguously determined by X-ray diffraction (XRD) analysis of compound **3ea** as a representative. (Figure 2)[13] Apart from the 2-arylthiazole derivatives, the commercially available 2-methylthiazole

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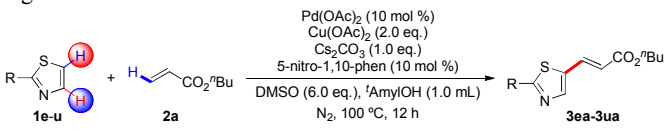
(**3ta**) and 2-(methylthio)thiazole (**3ua**) could also be applied to the reaction system, which afforded the alkenylated products in moderate yields (46% and 53%, respectively) and in a highly regioselective and stereoselective manner.



R = C_6H_5, **3ea**, 64% yield
4-MeO-C_6H_4, **3fa**, 66% yield
3-MeO-C_6H_4, **3ga**, 35% yield
2-MeO-C_6H_4, **3ha**, 77% yield
3-Me-C_6H_4, **3ia**, 88% yield
2-Me-C_6H_4, **3ja**, 75% yield
3,5-Me_2-C_6H_3, **3ka**, 70% yield
4-*i*-Pr-C_6H_4, **3la**, 53% yield
4-*t*-Bu-C_6H_4, **3ma**, 78% yield
R = 4-F-C_6H_4, **3na**, 65% yield
4-Cl-C_6H_4, **3oa**, 54% yield
4-CF_3-C_6H_4, **3pa**, 52% yield
2-Me-4-MeO_2C-C_6H_4, **3qa**, 46% yield
4-CN-C_6H_4, **3ra**, 39% yield
4-NO_2-C_6H_3, **3sa**, 22% yield
Me, **3ta**, 46% yield
MeS, **3ua**, 53% yield

Scheme 3 Regioselective and Stereoselective Alkenylation of 2-Substituted Thiazole Derivatives.

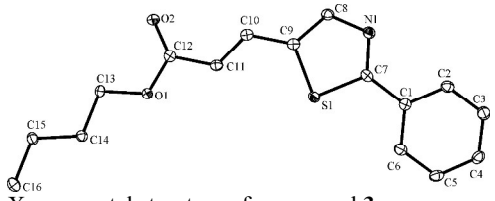
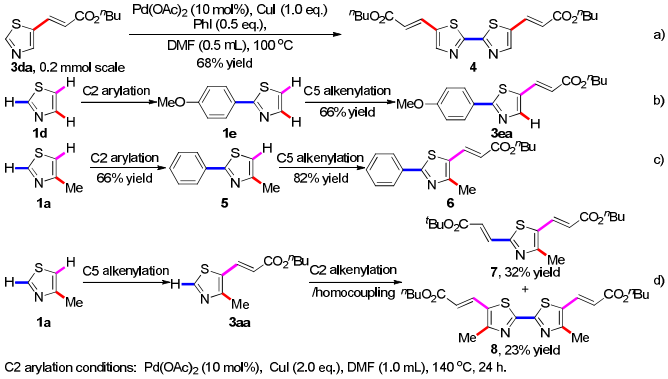


Figure 2 X-ray crystal structure of compound **3ea**.

To demonstrate the synthetic utility of this developed methodology, we then applied it to the diversified syntheses of thiazole-containing derivatives. At first, the 5-alkenylated thiazole derivative **3da** was used to carry out the homo-coupling reaction. As expected, this reaction proceeded smoothly in the presence of 10 mol % of $Pd(OAc)_2$, 1.0 equiv of CuI and 0.5 equiv of phenyl iodide with *N*,*N*-dimethyl formamide as the reaction media at 100 °C, affording the dimerized product in 68% yield (Scheme 4, eq. a). Moreover, starting from the commercially available thiazole **1d**, 5-alkenyl-2-arylthiazole **3ea** could be facilely obtained *via* a two-step sequence. By analogy, 5-alkenyl-2-aryl-4-methylthiazole **6** could be easily synthesized in good yields starting from 4-methylthiazole **1a**. Finally, a sequential installation of an alkenyl group has also been achieved by using 4-methylthiazole as a feedstock, the 2,5-differently alkenylated 4-methylthiazole derivative **7** was synthesized, together with the formation of applicable 2,2'-homo-coupling product **8** in synthetically useful yield.



Scheme 4 Divergent and Sequential Syntheses of Multifunctionalized Thiazole Derivatives.

Experimental procedure for the regioselective alkenylations

To a flame dried 25 mL Schlenk tube were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol; Acros), 5-nitro-1,10-phenanthroline (4.5 mg, 0.02 mmol; TCI), $Cu(OAc)_2$ (72.0 mg, 0.40 mmol; Acros) and Cs_2CO_3 (65.2 mg, 0.40 mmol; Ourchem), then the tube was capped with rubber stopper and alternatively extracted under vacuum pump and backfilled with nitrogen gas for three times. Then ^{t}AmylOH (1.0 mL or 2.0 mL, Alfa Aesar) was added *via* a syringe followed by sequential addition of DMSO (85.2 μL, 1.20 mmol, unpurified) and *n*-butyl acrylate (**2a**, 0.50 mmol). Finally, a solution of 4-methylthiazole (**1a**, 0.20 mmol, J&K) in ^{t}AmylOH (0.5 mL) was introduced intermittently (0.1 mL every hour) after the tube was placed on the preheated parallel reactor (100 °C). The reaction mixture was stirred at 100 °C for 12 h. After completion of the reaction, the reaction mixture was directly filtered by a short silica pad and further purified by flash column chromatography to afford (**3aa**, 31.5 mg, 70% yield) as colorless oil.

Conclusions

In conclusion, we have developed a regioselective and stereoselective alkenylation of thiazole derivatives and application of this established method to the divergent and programmed syntheses of multifunctionalized thiazole derivatives has also been successfully demonstrated. This research could provide a feasible solution for the fast establishment of thiazole-containing small molecule library. Moreover, toward the fluorescent materials syntheses, especially those incorporating the thiazole moiety, this research could provide a new approach for their syntheses. Therefore, screening of these synthesized thiazole derivatives from biological activity aspect and further application of this method in the syntheses of fluorescent materials are underway in our laboratory.

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