Tetrahedron Letters 52 (2011) 5643–5647

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium(II)-catalyzed oxidative Heck coupling of thiazole-4-carboxylates

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ARTICLE INFO

Article history:
Received 19 June 2011
Revised 28 July 2011
Accepted 16 August 2011
Available online 22 August 2011

Keywords:
Thiazole-4-carboxylate
C–H bond activation
Oxidative Heck-coupling
Alkenylation
Direct arylation

ABSTRACT

Oxidative Heck coupling of thiazole-4-carboxylates via palladium(II)-catalyzed C–H bond activation has been achieved in moderate to good yields. No ligand, and no acidic additive were used in the reaction. The results showed that this protocol tolerated a series of substitutions on the thiazole ring. A preliminary attempt of direct arylation with *p*-xylene via Pd(II)-catalyzed C–H bond activation has also been done.

Thiazole is among the most significant moieties in many natural products and synthetic molecules with potent biological activities. During the past decades, natural and synthetic thiazole-based molecules have drawn increasing attentions and interests due to their miscellaneous applications in pharmaceutical sciences and material chemistry. Among them, a variety of compounds featured with 5-vinylthiazole-4-carboxylate moiety[1] (Fig. 1a) and other 5-alkylthiazole-4-carboxylate moiety (Fig. 1b),[2] which could be derived from 5-vinyl substituted ones, have been reported to possess considerable biological activities. Thus, developing an efficient methodology on the alkenylation of thiazole-4-carboxylates is desirable.

During the last few decades, major progress has been achieved in transition-metal-catalyzed C–C bond-formation where one or both of the carbon atoms are required to be preactivated,[3] such as Mizoroki–Heck reaction and Suzuki–Miyaura coupling. More recently, direct C–C bond formation via palladium(II) catalyzed C–H bond cleavage of both substrates has been becoming an exceedingly valuable process in contemporary organic synthesis,[4] allowing concise and economical routes to be applied to the preparation of natural or synthetic compounds with biological activities. In light of the advances in this area, several groups have independently reported the cross-coupling reactions of thiazoles at 5-postion[5] with organic halides or acrylates. For example, Liegault and Fagnou et al.[5c,d] developed elegant palladium-catalyzed hetereoarene benzylation and heteroaromatic direct arylation, respectively. More recently, Miura et al. successfully achieved in 5-alkenylation of 2-substituted or 2,4-disubstituted thiazoles via Pd(II)-catalyzed C–H bond activation, in which EtCOOH or PivOH was used to accelerate the reaction.[6] Although their results shed some lights on direct C–H functionalization at 5-position of thiazoles, the direct alkenylation of thiazole-4-carboxylates at 5-position remains unexplored so far. As a continuation of our research on azoles,[7] hererin, we wish to report an acidic additive free palladium(II)-catalyzed oxidative Heck coupling of thiazole -4-carboxylates.

We began our investigation using **1a** as the model substrate. The results were summarized in Table 1. Initial attempts to evaluate different combinations of catalysts and oxidants indicated that a catalytic amount (20 mol %) of $Pd(OAc)_2$ with 2 equiv of AgOAc and olefin **2** (6 equiv) in DMF/DMSO (10:1, v/v) at 100 °C for 48 h could afford the desired alkenylation product **3a** in moderate yield (entry 1). $Cu(OAc)_2$ could also be used as an oxidant, but significant amount of homocoupling product **3a**′ was found as a side product (entry 2). Changing the oxidant or catalyst dramatically decreased the yields of **3a** (entries 3–5). The unsatisfactory yields were caused either by incomplete consumption of **1a** or generation of **3a**′. We then carefully screened the reaction conditions in order to improve the yields of **3a**. Very interestingly, the yield of **3a** was improved when the reaction was carried out at 110 °C with lower loading of $Pd(OAc)_2$ (10 mol %) (entry 6). Further tests on the reaction temperature revealed that an excellent yield of **3a** could be achieved when the reaction was performed at 115 °C (entry 7). Elevating temperature provided no better result (entry 8).

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doi:10.1016/j.tetlet.2011.08.088

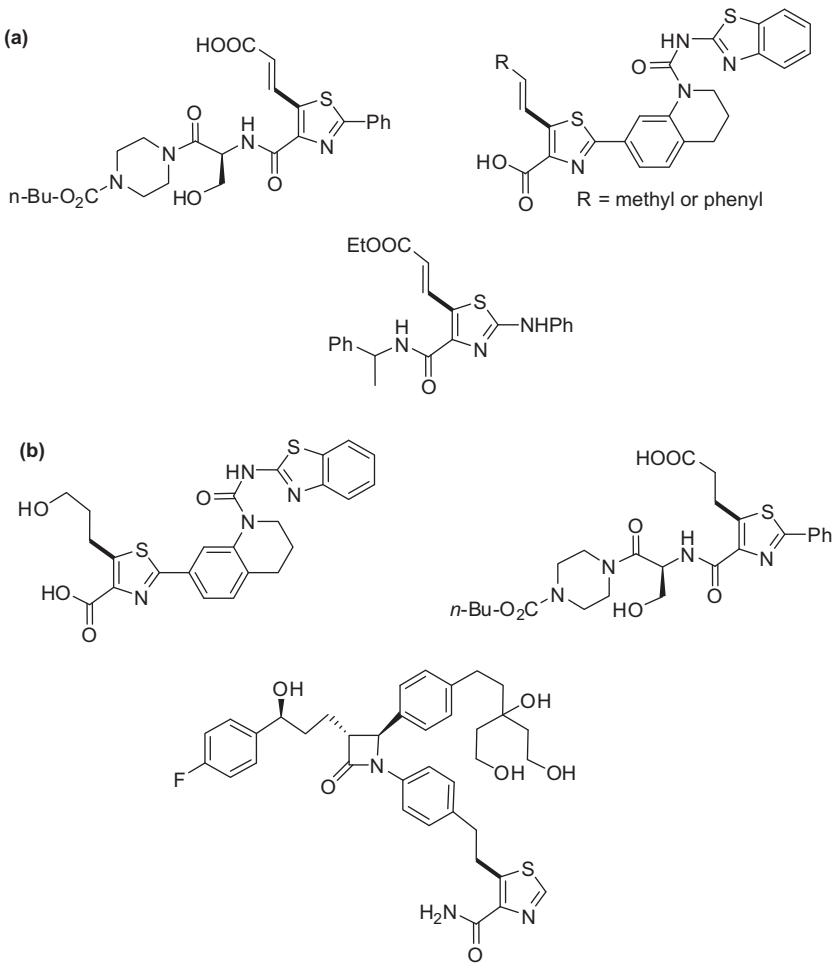


Figure 1. Representive biologically active compounds: (a) 5-vinylthiazole-4-carboxylates; (b) 5-alkylthiazole-4-carboxylates.

The excellent yield could also be maintained when the loading of **2** was gradually decreased to 1.5 equiv (entries 10–12), but remarkably dropped when the loading was declined to 1 equiv (entry 13). Thus, a condition of 1.5 equiv of **2**, 10 mol % of $Pd(OAc)_2$, 2 equiv of AgOAc at 115 °C in DMF/DMSO (10:1, v/v) was selected for further investigation of the substrate compatibility. Very gratifyingly, the formation of byproduct **3a′** was suppressed under this optimized condition.

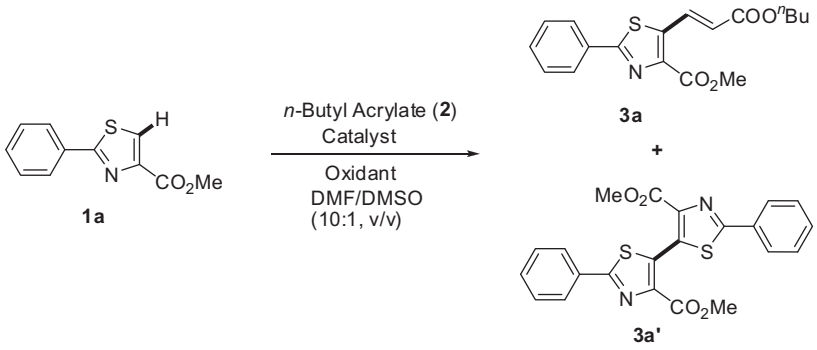
With the established condition in hand, we then examined a series of thiazole-4-carboxylates to demonstrate the substrate scope as shown in Table 2. Generally, all substrates reacted smoothly to provide the desired cross-coupling products in moderate to excellent yields within 48 h. Different substitutions on the thiazole ring were well tolerated, and some patterns were observed. For 2-phenyl substrates, the substrates with electron-donating group and halogen on the benzene ring afforded the product in good yields (**3a–3e**, **3h–3l**), while the ones with electron-withdrawing substituents gave the moderate yields due to incomplete consumption of the substrates (**3f–3g**). Only trace amount of the homocoupling byproducts could be observed for all 2-phenyl substrates, while more homocoupling byproducts for 2-alkyl and 2-carbonyl substituted substrates were obtained, leading to the relatively lower yields of the corresponding cross-coupling products (**3m–3o**).

Next, the effective condition was extended to a variety of olefins as shown in Table 3. Acrylates, acrylamide and styrene were well tolerated (**4a–4f**), affording the desired products in moderate to good yields, although small amount of substrates remained unconsumed even after 48 h. More bulky α-methylacrylates afforded the products only in lower yields and more homocoupling byproducts were isolated (**4e–4f**), suggesting that bulky olefins might be more difficult to couple with the thiazole substrates.

In addition, a preliminary attempt to couple thiazole-4-carboxylate with arene was conducted, since many compounds bearing 5-arylthiazole scaffold have been reported to have considerable pharmaceutical values. We successfully coupled methyl 2-phenylthiazole-4-carboxylate (**1a**) with *p*-xylene to afford the arylation product **5** in 35% yield. Most of **1a** was homocoupled to afford the byproduct **3a′** (Scheme 1). To the best of our knowledge, this is the first example that 5-arylation of thiazole via C–H bond cleavage of both substrates is ever reported. Further research focusing on the direct arylation is now undergoing in our group.

In conclusion, we have developed a general protocol for alkenylation of thiazole-4-carboxylates with good tolerance in moderate to excellent yields via $Pd(OAc)_2$-catalyzed C–H bond activation. The reaction demonstrated broad substrate and olefin scope. No pre-activation and no ligand or additive was required. This work could offer a route to the synthesis of 5-vinylthiazole-4-carboxylate scaffold-based biologically active compounds and other functional chemicals. Further application of this protocol to the synthesis of 5-vinylthiazole-4-carboxylate-based active com-

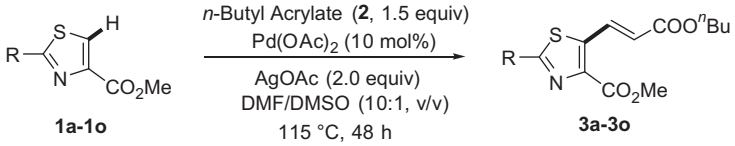
Table 1
Screening of reaction condition[a,8]

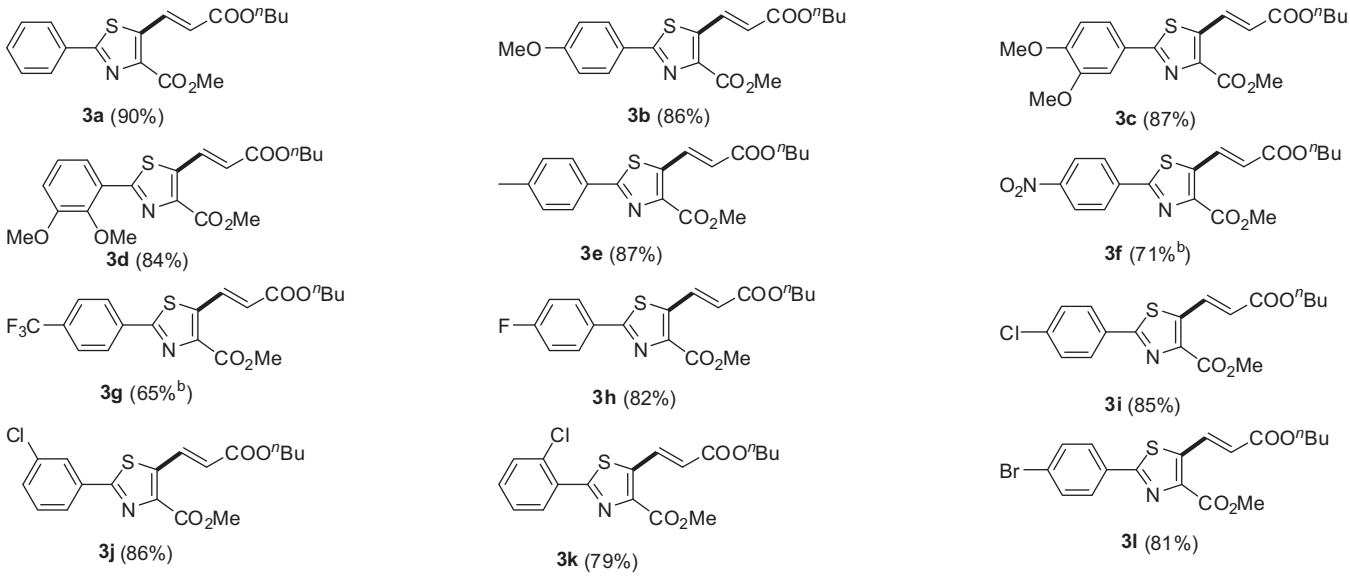


Entry	Catalyst (mol %)	Oxidant (equiv)	**2** (equiv)	Temp (°C)	Time (h)	Yields of **3a**/**3a'**[b] (%)
1	$Pd(OAc)_2$ (20)	AgOAc (2)	6	100	48	71/trace
2	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (2)	6	100	48	74/13
3	$Pd(OAc)_2$ (20)	Ag_2CO_3 (2)	6	100	48	48/trace[c]
4	$PdCl_2$ (20)	AgOAc (2)	6	100	36	55/4[d]
5	$PdCl_2$ (20)	$Cu(OAc)_2$ (2)	6	100	36	56/15
6	$Pd(OAc)_2$ (10)	AgOAc (2)	6	110	48	84/trace
7	$Pd(OAc)_2$ (10)	AgOAc (2)	6	115	48	90/trace
8	$Pd(OAc)_2$ (10)	AgOAc (2)	6	120	48	75/trace
9	$Pd(OAc)_2$ (5)	AgOAc (2)	6	115	48	86/trace
10	$Pd(OAc)_2$ (10)	AgOAc (2)	4	115	48	90/trace
11	$Pd(OAc)_2$ (10)	AgOAc (2)	2	115	48	88/trace
12	$Pd(OAc)_2$ (10)	AgOAc (2)	1.5	115	48	90/trace
13	$Pd(OAc)_2$ (10)	AgOAc (2)	1	115	48	78/19

[a] Reaction conditions: methyl 2-phenylthiazole-4-carboxylate (**1a**, 0.5 mmol), *n*-butyl acrylate (**2**), catalyst and oxidant in solvent (1.5 ml DMF with 0.15 ml DMSO).
[b] Isolated yield.
[c] 42% of **1a** was recovered.
[d] 37% of **1a** was recovered.

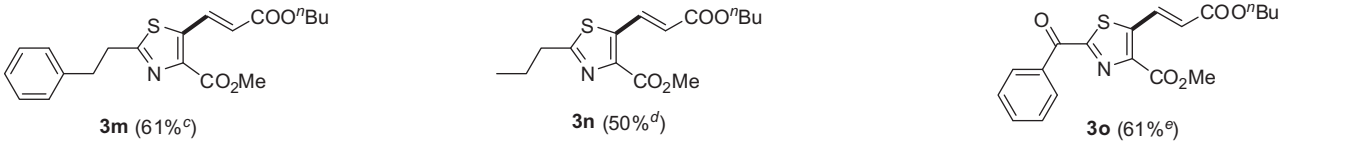
Table 2
Investigation on the substrate scope[a]





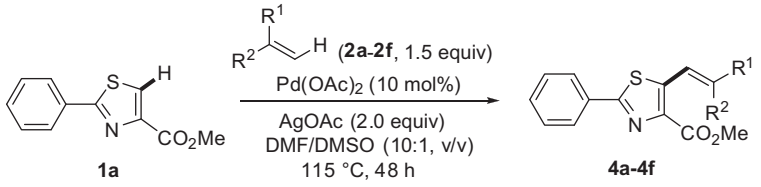
(*continued on next page*)

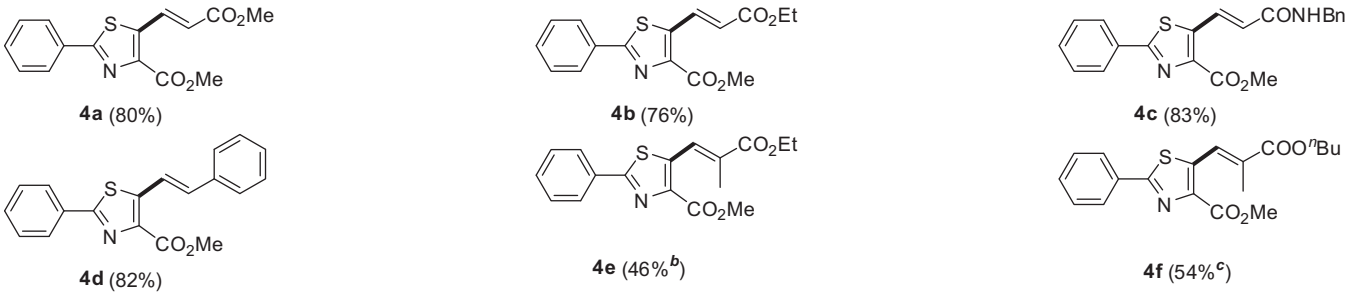
Table 2 (*continued*)



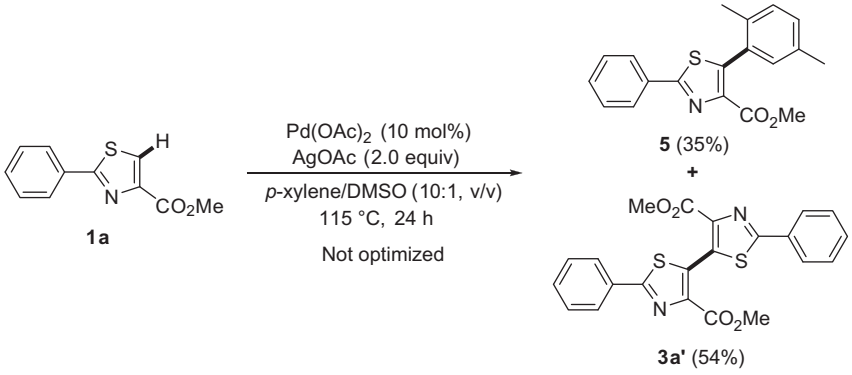
[a] Reaction conditions: methyl 2-substituted thiazole-4-carboxylate (**1a–1o**, 0.5 mmol), *n*-butyl acrylate (**2**, 0.75 mmol, 1.5 equiv), $Pb(OAc)_2$ (0.05 mmol, 10 mol%) and AgOAc (1 mmol, 2.0 equiv) in solvent (1.5 ml DMF with 0.15 ml DMSO) at 115 °C for 48 h. Isolated yields.
[b] Substrates incompletely consumed.
[c] With 30% of the homocoupling byproduct.
[d] With 38% of the homocoupling byproduct.
[e] With 32% of the homocoupling byproduct.

Table 3
Investigation on the olefin scope[a]





[b] With 49% of the homocoupling byproduct.
[c] With 38% of the homocoupling byproduct.
[a] Reaction conditions: methyl 2-phenylthiazole-4-carboxylate (**1a**, 0.5 mmol), olefins (**2a–2f**, 0.75 mmol, 1.5 equiv), $Pb(OAc)_2$ (0.05 mmol, 10 mol%) and AgOAc (1 mmol, 2.0 equiv) in solvent (1.5 ml DMF with 0.15 ml DMSO) at 115 °C. Isolated yields.



Scheme 1. A preliminary 5-arylation of **1a** via palladium catalyzed C–H bond cleavage of both substrates.

pounds as potential leads is undergoing in our laboratory and will be reported in due course.

Acknowledgments

Financial support from the Program for New Century Excellent Talents in University (NCET 2008) by the Ministry of Education of China, Fok Ying Tong Education Foundation (121040) and Fundamental Research Funds for the Central Universities (JKZ2009002 for H.Y.) is highly appreciated.

Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra of **3a–3o**, **4a–4f**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.088.

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8. *Typical procedure for palladium(II)-catalyzed oxidative Heck coupling of thiazole-4-carboxylate:* A reaction tube was charged with methyl 4-phenylthiazole-4-carboxylate (**1a**, 0.5 mmol), olefin **2** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 10 mol%), AgOAc (167 mg, 1 mmol, 2.0 equiv), DMF (1.5 ml) and DMSO (0.15 ml). The mixture was vigorously stirred at 115 °C (oil temperature). After stirring for 48 h, the mixture was cooled to room temperature, diluted with ethyl acetate and filtered. The filtrate was washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated in vacuo to give dark residue, which was purified by flash chromatography on silica gel to afford the cross coupling product **3a** (155 mg, 90%) as off-white solid; mp 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, 1H, J = 15.9 Hz), 7.96–8.00 (m, 2H), 7.46–7.49 (m, 3H), 6.36 (d, 1H, J = 15.9 Hz), 4.24 (t, 2H, J = 6.7 Hz), 4.02 (s, 3H), 1.66–1.74 (m, 2H), 1.39–1.49 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.7, 162.2, 144.9, 141.3, 133.6, 132.2, 131.4, 129.1, 127.1, 124.4, 64.9, 52.7, 30.7, 19.2, 13.7; IR (KBr) 2957, 2924, 2872, 2852, 1723, 1627, 1494, 1463, 1440, 1335, 1308, 1221, 1182, 1021, 973, 856, 769, 688, 643 cm^{-1}; HRMS (ESI) calcd for $[C_{18}H_{19}NO_4S+H]^+$ 346.1113, found 346.1117.