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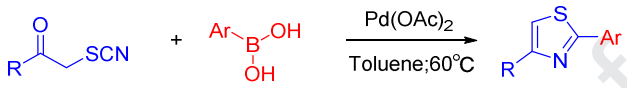

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ABSTRACT

A simple construction for various 2,4-disubstituted thiazoles *via* palladium(II)-catalyzed C(sp)–C(sp^2) and C-N cascade coupling reactions was developed. Various substrates can be tolerated with good yields. And its ligand-free condition demonstrates the practicability of this method.

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1. Introduction

Thiazoles and their derivatives are one of the most important classes of five-membered heteroaromatic compound exhibiting wide pharmacological applications. [1-4] Thiazole derivatives have attracted interest over the past years because of their broad biological activities such as anticancer,[5] anti-tubercular,[6] antihypertensive,[7] antimicrobial,[8-9] analgesic and anti-inflammatory.[10] In particular, 2,4-disubstituted thiazoles have been well known for their therapeutic applications and frequently utilized in bioactive compounds and pharmaceuticals, such as Fatostatin, p38 MAP kinase inhibitor and Fentiazac (Figure 1).[11-14]

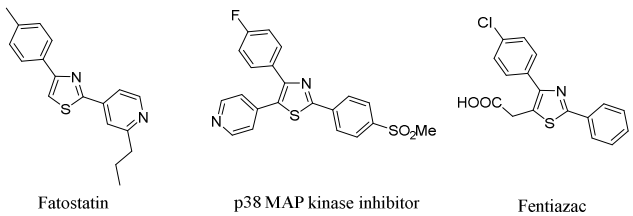

Figure 1. Selected examples of bioactive molecules based on 2,4-disubstituted thiazoles.

Owing to its diverse pharmaceutical applications, methodologies for construction of 2,4-disubstituted thiazoles have been extensively investigated. Nowadays, the most widely used synthetic method to access thiazoles is the Hantzsch thiazole synthesis reaction, [15-17] cyclization of α-haloaldehyde or ketone and thiourea or thioamide under neutral water-free conditions. [18] This reaction normally gives excellent yields for simple thiazoles but low yields for some substituted thiazoles. [19] Then, various methods for the synthesis of 2,4-disubstituted thiazoles have been developed (Scheme 1). Mahesh and co-workers reported a two-step reaction from styrene, NBS and thioamides to afford 2,4-disubstituted thiazoles. [20] The research by Kirchberg and co-workers reported palladium(II)-catalyzed biaryl coupling of thiazoles and boronic acids. [21] However, in this preparation method, the starting material already contains thiazole ring. Cosford and co-workers disclosed the synthesis of thiazole by using α-thiocyanomethyl ketones and aryl boric acid as starting material. [22] However, this is a three-step reaction using acids with lots of industrial wastes and pollution. Therefore, a more convenient construction for various 2,4-disubstituted thiazoles is still in demand.

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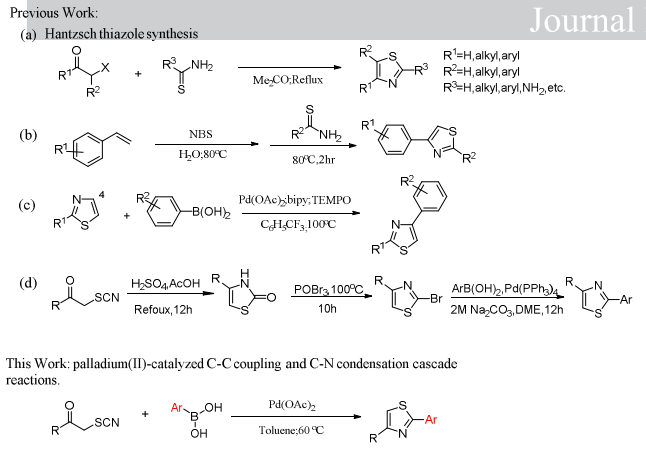
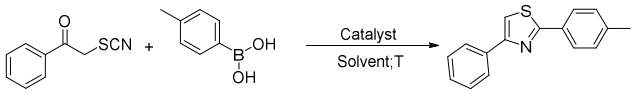


Scheme 1. Methods to the synthesis of 2,4-disubstituted thiazoles.

2. Results and discussion

Inspired by the work of predecessors, we proposed a palladium(II)-catalyzed tandem reaction for the synthesis of 2,4-disubstituted thiazoles. We first investigated the reaction of **1a** and **2a** in the presence of $Pd(OAc)_2$ (30 mol %) at 40 °C in toluene and obtained the major product **3a** (Table 1, entry 1). Then we changed the reaction temperature. When the reaction temperature was raised from 40 °C to 60 °C, the yield increased to 79% (Table 1, entries 1–2). While further increasing the reaction temperature, the yields decreased (Table 1, entries 3–5). In order to further improve the yields, we tested the reaction under the catalysis of a set of Pd (Table 1, entries 6–8). None of them showed more effective than $Pd(OAc)_2$. Additionally, other solvents, such as DMF, MeCN, EtOH and DMSO were tested (Table 1, entries 9–12). And toluene stood out as the best choice of solvent for further reactions with its highest product yield (Table 1, entry 2). Decreasing catalyst loading or amount of 4-methylphenylboric acid **2a** resulted in the reduced yields (Table 1, entries 13 and 15). And increasing catalyst loading to 40% or amount of 4-methylphenylboric acid **2a** to 2.5 equivalents did not have a significant effect on the yields (entries14 and 16). On the basis of the above studies, the most favorable reaction conditions for the formation of **3a** were established (Table 1, entry 2).

Table 1. Optimization of the reaction conditions for **3a**.



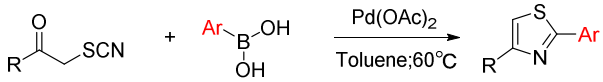
Entry[a]	catalyst	Equiv 1a:2a	T/°C	solvent	yield (%)[b]
1	$Pd(OAc)_2$	1:2.0	40	Toluene	73
2	$Pd(OAc)_2$	1:2.0	60	Toluene	79
3	$Pd(OAc)_2$	1:2.0	80	Toluene	60
4	$Pd(OAc)_2$	1:2.0	100	Toluene	56
5	$Pd(OAc)_2$	1:2.0	Reflux	Toluene	44
6	$Pd(PPh_3)_2Cl_2$	1:2.0	60	Toluene	24
7	$Pd(PPh_3)_4$	1:2.0	60	Toluene	15
8	–	1:2.0	60	Toluene	Trace
9	$Pd(OAc)_2$	1:2.0	60	DMF	55
10	$Pd(OAc)_2$	1:2.0	60	MeCN	25
11	$Pd(OAc)_2$	1:2.0	60	EtOH	Trace
12	$Pd(OAc)_2$	1:2.0	60	DMSO	28
13 [c]	$Pd(OAc)_2$	1:2.0	60	Toluene	51
14 [d]	$Pd(OAc)_2$	1:2.0	60	Toluene	80
15	$Pd(OAc)_2$	1:1.5	60	Toluene	62
16	$Pd(OAc)_2$	1:2.5	60	Toluene	78

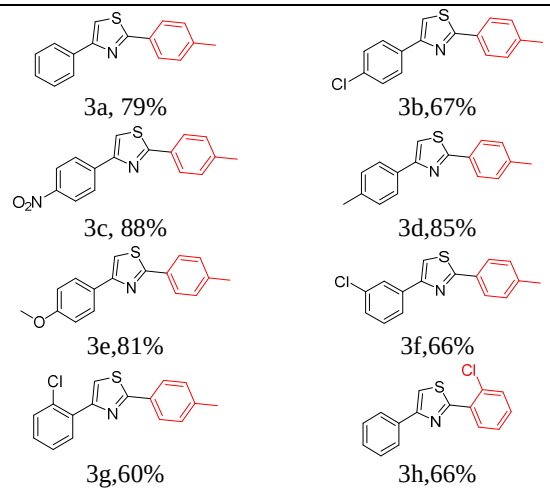
[a] Reaction conditions: **1a** (1.0 mmol), catalyst (30 mol %), solvent (15 mL), 24 h in air. [b] Isolated yield. [c] 20 mol % $Pd(OAc)_2$ catalyst was used. [d] 40 mol % $Pd(OAc)_2$ catalyst was used.

With the optimized reaction conditions in hand, the scope of the reaction was then explored. As shown in Table 2 the optimized reaction conditions can be applied to a variety of substrates. In terms of electronic effects, α-thiocyanomethyl ketones containing either electron-deficient groups (**3b**–**3c**) or electron-rich groups (**3d**–**3e**) on the phenyl ring were all compatible with this reaction (with 67% to 88% yield, Table 2). The results indicate that the electronic nature of α-thiocyanomethyl ketones has a little effect on the reaction yields. So we next investigated the steric effects of the reaction. A steric hindrance effect was observed when the chlorine atom was substituted at the *ortho*-position of the phenyl ring. And the desired product was obtained in a relatively lower yield (**3b**,**3f** and **3g**, 67%, 66% and 60%).

Based on these promising initial results, we then turned our attention toward the scope of arylboronic acids in this reaction. As expected, arylboronic acids with electron-donating group on the phenyl ring showed more reactivity than those electron-withdrawing groups (**3j**, 71% compared to **3m**, 81% and **3a**, 79%, Table 2). The reaction barely proceeded (**3k**) when (4-(trifluoromethyl)phenyl) boronic acid, with a strong electron-withdrawing group, was used. Changing the position of chlorine atom on the phenyl ring (**3h**-**3j**), the results showed that the steric effects almost did not influence the progress of the reaction (**3h**,**3i** and **3j**, 66%, 68% and 71%). In order to further expand the compound library, we synthesized a series of compounds with other groups, such as tert-butyl group and thiophene group with high yields (**3n**,68% and **3o**,73%). However, methyl boric acid was not compatible with this process (**3r**), probably due to its low activity.

Table 2. Synthesis of 2,4-disubstituted thiazoles. [a, b]





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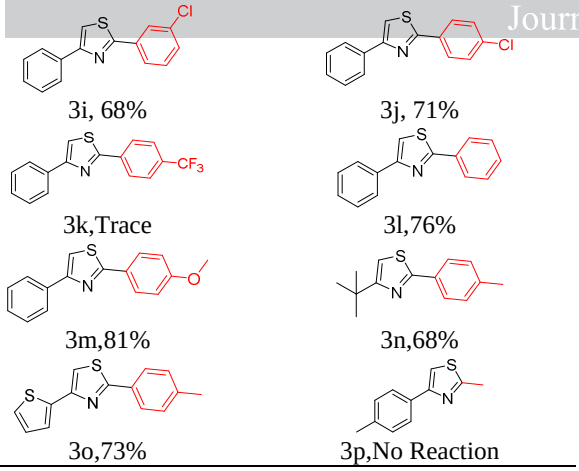
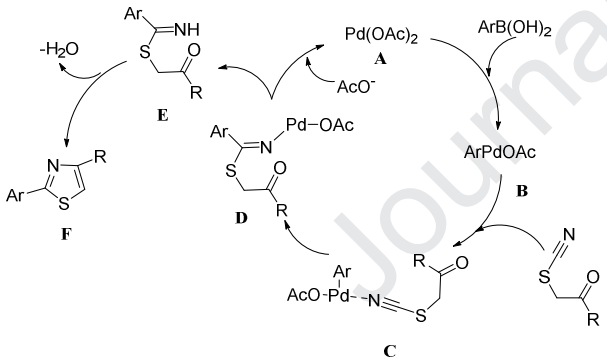


[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $Pd(OAc)_2$ (30 mol %), toluene (15 mL), 60 °C, 24 h in air. [b] Isolated yield.

A tentative mechanism for the construction of various 2,4-disubstituted thiazoles has been proposed (Scheme 2).[23] In the process of producing 2,4-disubstituted thiazoles, the transmetalation reaction of the Pd(II) catalyst and arylboronic acids affords intermediate **B**. Afterwards the coordination of intermediate **B** and the N atom of the cyano group forms compound **C**. Then the aryl group inserts into the nitrile group to generate the corresponding ketimine Pd(II) complex **D**. Intermediate **D** exchanges with AcO^- to produce ketimine derivative **E,** and thus regenerates the Pd(II) catalyst. Finally, the intramolecular condensation of ketimine derivative **E** affords the corresponding product **F**.



Scheme 2. Proposed Mechanism.

3. Conclusions

In summary, an e□cient method to access 2,4-disubstituted thiazoles through palladium(II)-catalyzed was demonstrated. The reaction involves C(sp)–C(sp^2) coupling followed by intramolecular C–N bond formation. The plausible mechanism was also proposed. The reaction can tolerate various substrates with good yields. Notably, this reaction is a palladium(II)-catalyzed but without any ligand progress. Because of its ligand-free condition, this method is particularly attractive.

4. Experimental section

4.1. General experimental information

All solvents were purified according to standard methods prior to use. Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t= triplet, q=quartet, m=multiplet), and coupling constant(s) in Hertz. For ^{13}C NMR, TMS (δ=0) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS. The starting material α-thiocyanomethyl ketones was prepared according to literature methods. [24] The starting material arylboronic acids were commercially available.

4.2. General Procedure for the Synthesis of 3

A mixture of α-thiocyanomethyl ketones **1** (1.0 mmol, 1.0 equiv.), arylboronic acids **2** (2.0 mmol, 2.0 equiv.) and $Pd(OAc)_2$ (0.3 mmol, 0.3 equiv.) was stirred in toluene (15.0 mL) at 60 °C for 24h. After the completeness of the reaction, the mixture was filtrated with diatomite. The solids were rinsed with EtOAc (2mLx3), and the combined filtrate was concentrated in vacuo and purified by flash column chromatography using PE and EtOAc as eluent to yield **3a-3o**.

4.3. Characterization Data of 3a-3o

4.3.1. 4-phenyl-2-(p-tolyl) thiazole (3a)

Pale yellow solid; mp: 125.7-126.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.37 – 7.30 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 2.40 (s, 3H); HRMS (ESI): m/z calcd for $C_{16}H_{13}NS$ [M+H]$^+$: 252.0841, found: 252.0845.

4.3.2. 4-(4-chlorophenyl)-2-(p-tolyl) thiazole (3b)

Yellow solid; mp: 141.4-142.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.66 (s, 1H), 7.29 (d, J = 7.5 Hz, 2H), 2.42 (s, 3H); HRMS (ESI): m/z calcd for $C_{16}H_{12}N_2O_2S$ [M+H]$^+$: 297.0692, found: 297.0697.

4.3.3. 4-(4-nitrophenyl)-2-(p-tolyl) thiazole (3c)

Yellow solid; mp: 141.4-142.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.66 (s, 1H), 7.29 (d, J = 7.5 Hz, 2H), 2.42 (s, 3H); HRMS (ESI): m/z calcd for $C_{16}H_{12}N_2O_2S$ [M+H]$^+$: 297.0692, found: 297.0697.

4.3.4. 2,4-di-p-tolylthiazole (3d)

White solid; mp: 139.4-140.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.39 (s, 1H), 7.27 (d, J = 5.0 Hz,2H), 7.25 (d, J = 6.0 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H); HRMS (ESI): m/z calcd for $C_{17}H_{15}NS$ [M+H]$^+$: 266.0998, found: 266.0998.

4.3.5. 4-(4-methoxyphenyl)-2-(p-tolyl) thiazole (3e)

Pale yellow solid; mp: 150.0-150.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 4H), 7.31 (s, 1H), 7.26 (d, J = 8.0 Hz, 3H), 6.97 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H), 2.41 (s, 3H).; HRMS (ESI): m/z calcd for $C_{17}H_{15}ONS$ [M+H]$^+$: 282.0947, found: 282.0951.

4.3.6. 4-(3-chlorophenyl)-2-(p-tolyl) thiazole (3f)

Light pink solid; mp: 85.0-85.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (t, J = 2.0 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.87 – 7.83 (m, 1H), 7.47 (s, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.33-7.31 (m, 1H), 7.27 (d, J = 7.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.38, 154.62, 140.53, 136.31, 134.73, 130.92, 129.97, 129.66, 128.07, 126.63, 126.56, 124.45, 113.11, 21.48; HRMS (ESI): m/z calcd for $C_{16}H_{12}ClNS$ [M+H]$^+$: 286.0452, found: 286.0458.

4.3.7. 4-(2-chlorophenyl)-2-(p-tolyl) thiazole (3g)

Pale yellow solid; mp: 54.6-55.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.0, 2.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.48 (dd, J = 8.0, 1.0 Hz, 1H), 7.37 (td, J = 7.5, 1.0 Hz, 1H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.03, 152.44, 140.48, 133.38, 132.08, 131.79, 131.01, 130.58, 129.74, 129.09, 127.09, 126.67, 117.65, 21.60; HRMS (ESI): m/z calcd for $C_{16}H_{12}ClNS$ $[M+H]^+$: 286.0452, found: 286.0450.

4.3.8. 2-(2-chlorophenyl)-4-phenylthiazole (3h)

Yellow solid; mp: 53.9-54,8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, J = 7.5, 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 1.0 Hz, 2H), 7.65 (s, 1H), 7.52 (dd, J = 8.0, 2.0 Hz, 1H), 7.47 (m, J = 7.5 Hz, 2H), 7.42 – 7.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.30, 155.10, 134.51, 132.15, 132.13, 131.18, 130.80, 130.43, 128.90, 128.35, 127.20, 126.61, 114.73; HRMS (ESI): m/z calcd for $C_{15}H_{10}ClNS$ $[M+H]^+$: 272.0295, found: 272.0297.

4.3.9. 2-(3-chlorophenyl)-4-phenylthiazole (3i)

Pale brown solid; mp: 59.9-60.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.00 (d, J = 7.0 Hz, 2H), 7.90 (td, J = 7.0, 1.5 Hz, 1H), 7.51 (s, 1H), 7.46 (t, J = 7.0 Hz, 2H), 7.41 – 7.35 (m, 3H); HRMS (ESI): m/z calcd for $C_{15}H_{10}ClNS$ $[M+H]^+$: 272.0295, found: 272.0295.

4.3.10. 2-(4-chlorophenyl)-4-phenylthiazole (3j)

White solid; mp: 95.0-95.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.93 (m, 4H), 7.50 – 7.41 (m, 5H), 7.37 (t, J = 7.0 Hz, 1H).; HRMS (ESI): m/z calcd for $C_{15}H_{10}ClNS$ $[M+H]^+$: 272.0295, found: 272.0287.

4.3.11. 2,4-diphenylthiazole (3l)

White solid; mp: 93.7-94.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.0, 1.5 Hz, 2H), 8.01 (dd, J = 8.5, 1.5 Hz, 2H), 7.50 – 7.44 (m, 6H), 7.37 (t, J = 7.0 Hz, 1H).; HRMS (ESI): m/z calcd for $C_{15}H_{11}NS$ $[M+H]^+$: 238.0685, found: 238.0692.

4.3.12. 2-(4-methoxyphenyl)-4-phenylthiazole (3m)

White yellow solid; mp 100.5-101.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 4H), 7.45 (t, J = 7.5 Hz, 2H), 7.41 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H); HRMS (ESI): m/z calcd for $C_{16}H_{14}NOS$ $[M+H]^+$:268.0791, found: 268.0791.

4.3.13. 4-(tert-butyl)-2-(p-tolyl) thiazole (3n)

Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 7.5 Hz, 2H), 6.84 (s, 1H), 2.39 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.66, 167.17, 139.80, 131.76, 129.58, 126.57, 109.84, 35.07, 30.23, 21.55; HRMS (ESI): m/z calcd for $C_{14}H_{17}NS$ $[M+H]^+$: 232.1154, found: 232.1159.

4.3.14. 4-(thiophen-2-yl)-2-(p-tolyl) thiazole (3o)

Pale purple solid; mp: 109.6-110.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.51 (dd, J = 4.0, 1.5 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.26 (d, J = 7.5 Hz, 2H), 7.08 (dd, J = 5.0, 4.0 Hz, 1H), 2.41 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.30, 150.70, 140.59, 138.62, 130.89, 129.73, 127.81, 126.69, 125.37, 124.29, 111.04, 21.62; HRMS (ESI): m/z calcd for $C_{14}H_{11}NS_2$ $[M+H]^+$: 258.0406, found: 258.0413.

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Supplementary Material

Supplementary data (Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products.) associated with this article can be found in online version at http://dx.doi.org/.

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- A simple construction for various 2,4-disubstituted thiazoles.
- The reaction involves C(sp)–C(sp^2) coupling followed by intramolecular C–N bond formation.
- Various substrates can be tolerated with good yields in ligand-free condition.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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