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Communication

Highly regioselective ruthenium-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles with aryl iodides and aryl bromides via C–H bond activation

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ABSTRACT

We have developed a convenient ruthenium-catalyzed direct arylation for highly regioselective synthesis of thiazolo[3,2-*b*]-1,2,4-triazole derivatives via C–H bond activation. This transformation has provided a new synthetic route to a variety of thiazolo[3,2-*b*]-1,2,4-triazoles and afforded desired products in good yields.

1. Introduction

Heteroaromatic compounds are an important class of building blocks found in a variety of areas, such as many natural products, medicines, and functional materials [1–3]. Therefore, the development of new transformation for direct and selective arylation to prepare heteroaromatic compounds is a persistent challenge for organic synthetic chemists. In the past few years, many successful and elegant transition-metal-catalyzed arylation of heterocycles via C–H bonds activation have been developed [4–13]. Among the metal catalysts, the palladium- [14–19], copper- [20–25], rhodium- [26–28], ruthenium- [29–41], nickel- [42–45] catalyzed arylation of heterocycles are the most important and convenient methods to construct complex heteroaromatic molecules. Although many synthetic routes for their construction have been developed, this field is still highly favorable. Exploration for efficient transition-metal-catalyzed direct arylation synthesis of heteroaromatic compounds continues to attract the interest of synthetic chemists.

The thiazolo[3,2-*b*]-1,2,4-triazole nucleus is arguably one of the most significant heterocycles since they are found in numerous natural products and bioactive molecules [46–48]. In particular, thiazolo[3,2-*b*]-1,2,4-triazole derivatives with a biaryl motif have been widely investigated as anti-inflammatory, antibacterials, anticancer, antimicrobial, and analgesic molecules [49–53] (Fig. 1). Generally, there are mainly four routes to prepare thiazolo[3,2-*b*]-1,2,4-triazole derivatives: (i) cyclization of 3-mercapto-1,2,4-triazoles with α-haloketones; (ii) cyclization of 2-imino-3-amino thiazoles with acids or anhydrides; (iii) cyclization of bis(1*H*-1,2,4-triazolyl)sulfoxide with chalcones; (iv) arylation of thiazolo[3,2-*b*]-1,2,4-triazoles [54–58]. Despite of several methodologies have been developed during the last decades, there have only been rare examples for metal-catalyzed arylation of thiazolo[3,2-*b*]-1,2,4-triazoles.

Herein, we reported our new finding which was a facile highly regioselective Ruthenium-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles with aryl halide in Scheme 1. To the best of our knowledge, this is the first example of the Ruthenium-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles.

2. Results and discussion

Initially, our efforts were focused on identifying the catalytic system and reaction conditions for direct arylation of 6-

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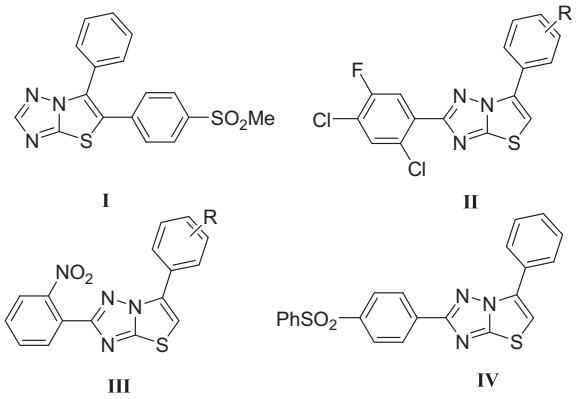
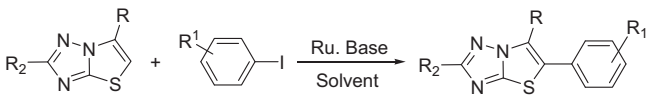


Fig. 1. Thiazolo[3,2-*b*]-1,2,4-triazole derivatives with biological activities.

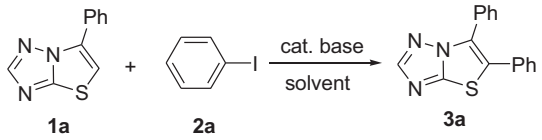
phenylthiazolo[3,2-*b*]-1,2,4-triazole **1a** with iodobenzene **2a**. A variety of Ruthenium-catalysts in conjunction with different bases, solvents and temperatures were tested and the results were described in Table 1. To our delight, the desired product 5,6-diphenylthiazolo[3,2-*b*]-1,2,4-triazole **3a** was formed in the presence of $[RuCl_2(p\text{-cymene})]_2$ and Na_2CO_3 in DMA at 120 °C for 12 h. After this, other Ruthenium catalysts, such as $RuCl_3(H_2O)_n$, $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$ and $Ru(acac)_2$, were also employed in reaction and the corresponding arylation product **3a** was obtained in 13%, 38%, 64% and 20% yields respectively (Table 1, entries 2–5). The results indicated that $Ru_3(CO)_{12}$ was the most efficient catalyst in this reaction. Next, the effects of bases were also tested in this arylation (Table 1, entries 6–10). Among a variety of inorganic bases, Cs_2CO_3 was proved to be the most suitable in present of $Ru_3(CO)_{12}$ in DMA at 120 °C. However, relative lower yields were obtained when the other bases were used, such as K_2CO_3, KH_2PO_4, *t*-BuONa and KOAc. We next attempted to improve the yields by using various solvents. As entries 11–15 of Table 1 indicated, NMP was the most effective media for this arylation process. The effects of temperature was also detected (Table 1, entries 16–18) and it was evident that 140 °C was the most optimal one for this $Ru_3(CO)_{12}$-catalyzed arylation. Finally, the control experiment results showed that product **3a** was not formed in the absence of $Ru_3(CO)_{12}$ by using Cs_2CO_3 as bases in NMP at 140 °C.

With the optimized conditions in hand, that is, thiazolo[3,2-*b*]-1,2,4-triazoles (0.5 mmol), aryl iodides (0.7 mmol), $Ru_3(CO)_{12}$ as the catalyst, Cs_2CO_3 as the bases and NMP as the solvent, we next turned our attention to the scope of the Ruthenium-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles with aryl iodides. As shown in Table 2, 6-substituted thiazolo[3,2-*b*]-1,2,4-triazoles were examined and the results showed that a variety of aryl iodides with either electron-donating or electron-withdrawing groups attached to the benzene rings, were able to undergo arylation smoothly and generated the corresponding products in good yields (**3a**–**3o**). As expected, the group (CF_3) on the phenyl ring of aryl iodides was compatible under this process, and the corresponding product was isolated in 80–81% yields. In addition, bromobenzene as a substrate was tested and the desired product was formed in 80% yields. All these cases showed high functional group tolerance (CH_3, F, Cl, Br, CF_3) for the arylation. Pleasingly, all reactions were very clean, and the sole arylation products were obtained with highly regioselective at C-5 position under our standard experimental conditions.



Scheme 1. Ru-catalyzed arylation of thiazolo[3,2-*b*]-1,2,4-triazole with aryl halide.

Table 1
Optimization of reaction conditions for the arylation of 6-phenylthiazolo[3,2-*b*]-1,2,4-triazole with iodobenzene.[a]



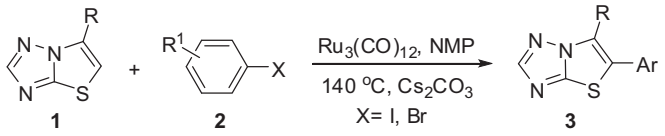
Entry	Catalyst (mol%)	Base	Solvent	T (°C)	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	Na_2CO_3	DMA	120	42
2	$RuCl_3(H_2O)_n$	Na_2CO_3	DMA	120	13
3	$RuCl_2(PPh_3)_3$	Na_2CO_3	DMA	120	38
4	$Ru_3(CO)_{12}$	Na_2CO_3	DMA	120	64
5	$Ru(acac)_2$	Na_2CO_3	DMA	120	20
6	$Ru_3(CO)_{12}$	K_2CO_3	DMA	120	67
7	$Ru_3(CO)_{12}$	Cs_2CO_3	DMA	120	76
8	$Ru_3(CO)_{12}$	KH_2PO_4	DMA	120	53
9	$Ru_3(CO)_{12}$	*t*-BuONa	DMA	120	37
10	$Ru_3(CO)_{12}$	KOAc	DMA	120	42
11	$Ru_3(CO)_{12}$	Cs_2CO_3	DMF	120	68
12	$Ru_3(CO)_{12}$	Cs_2CO_3	DMSO	120	65
13	$Ru_3(CO)_{12}$	Cs_2CO_3	NMP	120	84
14	$Ru_3(CO)_{12}$	Cs_2CO_3	1,4-dioxane	120	45
15	$Ru_3(CO)_{12}$	Cs_2CO_3	Toluene	120	41
16	$Ru_3(CO)_{12}$	Cs_2CO_3	NMP	140	87
17	$Ru_3(CO)_{12}$	Cs_2CO_3	NMP	160	86
18	$Ru_3(CO)_{12}$	Cs_2CO_3	NMP	100	55
19	–	Cs_2CO_3	NMP	140	–[c]

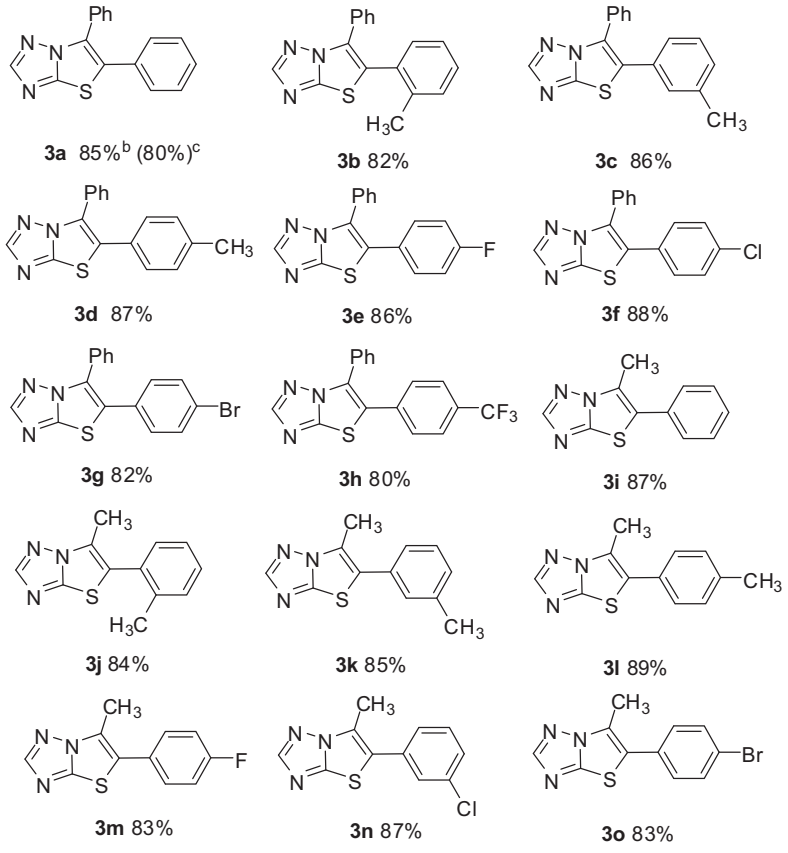
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), catalyst (3 mol%), base (1.0 mmol), solvent (2 mL), 100–160 °C, 12 h.
[b] GC yields.
[c] No product.

Subsequently, we were interested in evaluating the scope of this $Ru_3(CO)_{12}$-catalyzed arylation by using 2,6-disubstituted thiazolo[3,2-*b*]-1,2,4-triazoles as substrates and the results showed in Table 3. The reaction conditions had proven to be useful for a range of 2,6-disubstituted thiazolo[3,2-*b*]-1,2,4-triazoles. The reaction of 2,6-disubstituted thiazolo[3,2-*b*]-1,2,4-triazoles with differently substituted on the phenyl ring of aryl iodides, such as 4-CH_3, 2-CH_3, 2-F, 3-Cl and 4-CF_3, had a beneficial effect on the reaction outcomes, and in most cases the corresponding arylation products were obtained in good yields under the previously optimized conditions. These results indicated that all of the aryl iodides, regardless of their electronic or steric properties, proceeded smoothly in good yields to afford the expected arylation products.

A proposed mechanism of the direct arylation could be described in Scheme 2. A mechanism similar to those of previous arylation of heterocycles may be involved for the present reaction. First, $Ru_3(CO)_{12}$ reacted with aryl iodides to form Ru-complexes **A** which directed electrophilic attack on **1a** to generate the intermediate **B**. Subsequently, the deprotonation of intermediate **B** with the help of Cs_2CO_3 would give intermediate **C**, which would then undergo reductive elimination to form the **3** and release the Ru catalyst.

Table 2
Regioselective synthesis of thiazolo[3,2-*b*]-1,2,4-triazoles.[a]





[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), $Ru_3(CO)_{12}$ (3 mol%), Cs_2CO_3 (1.0 mmol), NMP (2 mL), 140 °C, 12 h; [b] Isolated yields; [c] Isolated yields by using **1a** and bromobenzene as substrates.

3. Conclusion

In summary, an efficient highly region selective $Ru_3(CO)_{12}$-catalyzed direct arylation of thiazolo[3,2-*b*]-1,2,4-triazoles with aryl iodides via C–H activation has been developed. This transformation provided a convergent approach for the formation of hetero-aryl bonds to prepare thiazolo[3,2-*b*]-1,2,4-triazole derivatives in good yields.

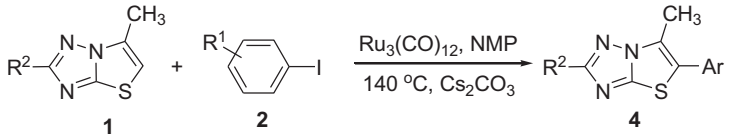
4. Experimental section

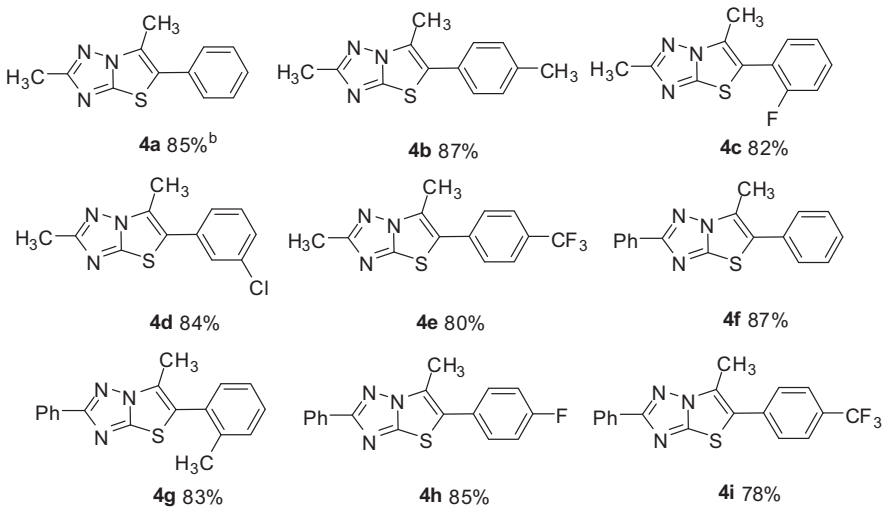
NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer (100 MHz for carbon) and respectively referenced to 7.26 and 77.0 ppm for chloroform-d solvent with TMS as internal standard. ESI-MS spectra were measured on Finnigan Mat TSQ 7000 instruments. Elemental analyses were performed on a Heraeus elemental analyzer. All the other chemicals were purchased from Aldrich Chemicals.

4.1. General procedure for the synthesis of *3a*

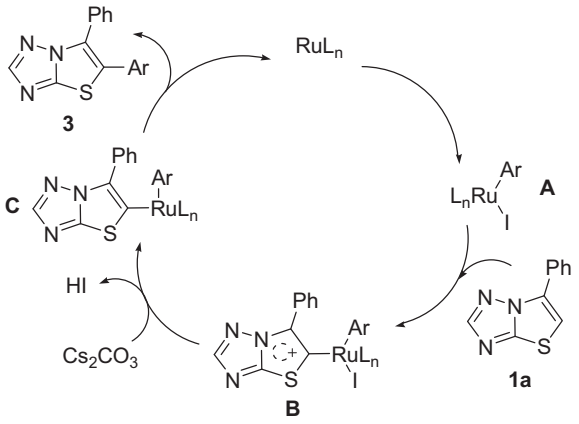
6-Phenylthiazolo[3,2-*b*]-1,2,4-triazole **1a** (0.5 mmol, 100.5 mg), iodobenzene **2a** (0.7 mmol, 142.8 mg), $Ru_3(CO)_{12}$ (3 mol%), and Cs_2CO_3 (1.0 mmol) were stirred in 2 mL of NMP at 140 °C for 12 h. After completion of the reaction (monitored by TLC), the water (15 mL) was added. The aqueous solution was extracted with ethyl acetate (3 × 10 mL) and the combined extract was dried with anhydrous Na_2SO_4. The solvent was removed and the crude product was separated by column chromatography (eluted with petroleum ether/ethyl acetate = 8:1) to give a pure product of **3a** (117.7 mg).

Table 3
Synthesis of thiazolo[3,2-*b*]-1,2,4-triazoles.[a]





[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), $Ru_3(CO)_{12}$ (3 mol%), Cs_2CO_3 (1.0 mmol), NMP (2 mL), 140 °C, 12 h; [b] Isolated yields.



Scheme 2. Plausible reaction mechanism.

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