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ORIGINAL PAPER

An efficient access to 2,3-diarylimidazo[1,2-*a*]pyridines via silver(I)-catalyzed C-H bond functionalization

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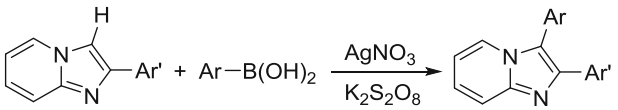
Abstract An efficient and economic Ag-catalyzed method for the direct cross-coupling of unactivated imidazo[1,2-*a*]pyridines with arylboronic acids has been developed. This approach leads to the formation of corresponding 2,3-diarylimidazo[1,2-*a*]pyridine derivatives as biological and pharmaceutical materials of interest in good yields under mild reaction conditions.

Graphical abstract



Keywords C–H activation reaction · Direct arylation · 2,3-Diarylimidazo[1,2-*a*]pyridines · Imidazo[1,2-*a*]pyridine

Introduction

During the recent decades, the transition-metal-catalyzed C-H bond activation reactions of heterocycles with aryl groups for the formation of heteroaromatic molecules have gained considerable importance among synthetic chemists [1–9]. Although different transition metals have been employed in these reactions, trying to find novel methods using inexpensive and highly efficient transition-metal catalysts is still attractive.

Imidazo[1,2-*a*]pyridines are one of the interesting biologically active nitrogen-containing heterocyclic compounds with a wide range of biological activities such as antiviral [10], antibacterial [11], antifungal [12, 13], antiprotozoal [14], antiherpes [15], and anti-apoptotic properties [16]. Imidazo[1,2-*a*]pyridine unit is an essential scaffold in a number of sedative and anxiolytic commercial drugs such as saripidem, necopidem, and alpidem (Fig. 1).

Regarding the remarkable biological activities of imidazo[1,2-*a*]pyridines, a number of synthetic routes for the construction of this valuable scaffold have been reported using a transition-metal-catalyzed cross-coupling reactions in the literature. For instance, in 2000, Enguehard et al. reported a Suzuki-type cross-coupling reaction on 2-substituted 3-iodoimidazo[1,2-*a*]pyridines to afford 2,3-diarylimidazo[1,2-*a*]pyridines [17]. In 2012, Cao et al. reported a copper-catalyzed direct C-3 arylation of 2-substituted imidazo[1,2-*a*]pyridines with aryl iodides, bromides, and triflates [18]. In 2013, Liu et al. reported a Rh-catalyzed C-H arylation of imidazo[1,2-*a*]pyridines with aryl halides or triflates [19]. In 2014, Zhao et al. reported a palladium-catalyzed cross-coupling of imidazo[1,2-*a*]pyridines with arylboronic acids [20]. In the same year, Wang et al. reported a palladium-catalyzed cross-coupling reaction of imidazo[1,2-*a*]pyridines with

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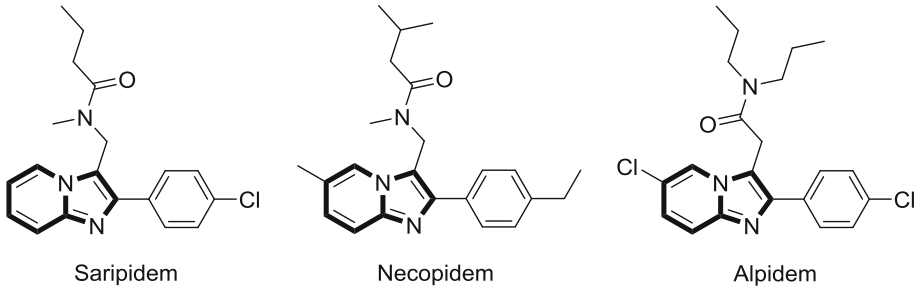
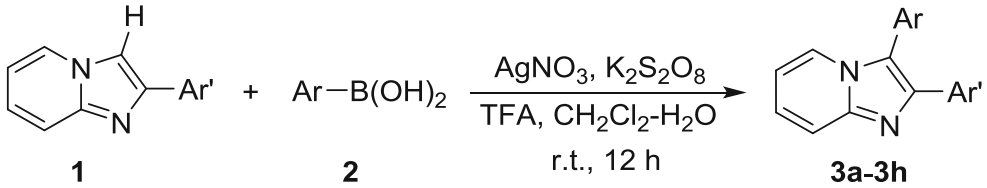


Fig. 1 Examples of commercially available imidazo[1,2-*a*]pyridine-based drugs

Scheme 1



arenes [21]. Also recently, a number of metal-catalyzed C–H activation arylation reactions on 2-substituted imidazo[1,2-*a*]pyridines to afford 2,3-disubstituted imidazo[1,2-*a*]pyridines are reported in the literature [22–28].

As can be concluded from the previous reports starting from imidazo[1,2-*a*]pyridines, some drawbacks such as using expensive transition-metal catalysts and being limited to use the halogen/triflate-bearing starting materials suppress the ease of making new compounds by directly starting from C–H target bonds. Therefore, introducing efficient, facile, and economical methods to achieve the direct C–H functionalization of target compounds to produce the corresponding cross-coupling products is of great importance. Hence, we herein described the first example of direct cross-coupling of imidazo[1,2-*a*]pyridines with arylboronic acids at C-3 position in the presence of $AgNO_3$ as an absolutely inexpensive catalyst under mild reaction conditions.

Results and discussion

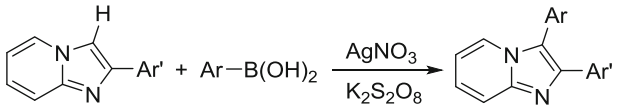
In continuation of our researches on preparation of N-containing heterocyclic compounds [29–32], herein, we report an efficient and economic approach for synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines **3a**–**3h** via direct Ag-catalyzed cross-coupling reaction of unactivated 2-arylimidazo[1,2-*a*]pyridines **1** with arylboronic acids **2** (Scheme 1).

To achieve the optimized reaction conditions, 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and phenylboronic acid (**2a**) were chosen as the model substrates (Table 1). The effects of different silver catalysts, oxidants, additives, and solvents were screened. We started our investigations by screening the formation of the desired coupling product in the presence of 10 mol% $AgNO_3$ as the catalyst, 1 equiv. of $K_2S_2O_8$ as the oxidant, and 1 equiv. of TFA as an additive in 6 cm^3 of CH_2Cl_2:H_2O with the ratio 1:1 at rt which led to 54% product yield (entry 1). Among the other examined silver(I) catalysts, $AgNO_3$ gave the highest yield in combination with $K_2S_2O_8$ as the oxidant. Using other silver(I) catalysts such as Ag_2CO_3 and Ag_2O decreased the reaction yield as well as other oxidants such as $Na_2S_2O_8$ and H_2O_2 (entries 2–5). We next examined the amounts of catalyst and oxidant with different ratios (entries 6–15). Finally, we studied the effect of the solvent on the reaction progress. The use of other solvents like CH_3CN:H_2O and acetone:H_2O dramatically suppressed the yield and were totally ineffective (entry 16, 17). It was clearly concluded that the best results were obtained with 20 mol% $AgNO_3$ and 3 equiv. of $K_2S_2O_8$, TFA as an additive in CH_2Cl_2:H_2O with the ratio 1:1 (entry 11).

With the optimized reaction conditions available for the Ag-catalyzed synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines, we investigated the substrates scope. Different 2-arylimidazo[1,2-*a*]pyridines with various aryl boronic acids were examined, and the results are summarized in Table 2. As shown in Table 2, different electron-donating and electron-withdrawing substituents on the aryl ring of arylboronic acids were tolerated and the resulting corresponding products **3a**–**3h** were obtained in good yields.

On the basis of the previous reports, a plausible mechanism for the formation of 2,3-diarylimidazo[1,2-*a*]pyridines **3** is given in Scheme 2. It has been reported

Table 1 Effect of different reaction conditions on synthesis of 2,3-diphenylimidazo[1,2-*a*]pyridine



Entry	Catalyst	Oxidant	Additive	Solvent	Yield/%[a]
1	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	54
2	Ag_2CO_3	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	48
3	Ag_2O	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	43
4	$AgNO_3$	$Na_2S_2O_8$	TFA	CH_2Cl_2/H_2O	50
5	$AgNO_3$	H_2O_2	TFA	CH_2Cl_2/H_2O	10
6[b]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	64
7[c]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	58
8[d]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	40
9[e]	$AgNO_3$	$K2S_2O_8$	TFA	CH_2Cl_2/H_2O	34
10[f]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	53
11[g]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	71
12[h]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	50
13[i]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	35
14[j]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	48
15[k]	$AgNO_3$	$K_2S_2O_8$	TFA	CH_2Cl_2/H_2O	61
16	$AgNO_3$	$K_2S_2O_8$	TFA	CH_3CN/H_2O	Trace
17	$AgNO_3$	$K_2S_2O_8$	TFA	Acetone/H_2O	Trace

Reaction conditions: 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 1 mmol), phenylboronic acid (**2a**, 1.5 mmol), catalyst (10 mol%), oxidant (1 eq.), TFA (1 eq), solvent (1:1), rt, 12 h

[a] Isolated yields

[b] Catalyst (10 mol%), oxidant (2 eq.)

[c] Catalyst (10 mol%), oxidant (3 eq.)

[d] Catalyst (10 mol%), oxidant (4 eq.)

[e] Catalyst (20 mol%), oxidant (1 eq.)

[f] Catalyst (20 mol%), oxidant (2 eq.)

[g] Catalyst (20 mol%), oxidant (3 eq.)

[h] Catalyst (20 mol%), oxidant (4 eq.)

[i] Catalyst (30 mol%), oxidant (1 eq.)

[j] Catalyst (30 mol%), oxidant (2 eq.)

[k] Catalyst (30 mol%), oxidant (3 eq.)

[33–35] that persulfate anion in the presence of Ag(I) disproportionates into sulfate radical anion, sulfate dianion, and Ag(II) ion. Next, arylboronic acid, through the reduction of Ag(II) into Ag(I), provides an aryl radical. This aryl radical could react with the protonated imidazopyridine **A** to give radical cation **B**. Then, a hydrogen atom can be removed from radical cation **B** by sulfate radical anion to produce protonated imidazopyridine **C**. Finally, the desired product **3** can be afforded after a basic workup (Scheme 2).

In conclusion, we have developed a novel, facile, and economic Ag-catalyzed direct cross-coupling reaction of unactivated imidazo[1,2-*a*]pyridines with arylboronic acids for the first time. The present method represents an efficient way to produce the corresponding imidazo[1,2-*a*]pyridine derivatives in good yields under mild reaction conditions.

Experimental

All chemicals were purchased from Merck and Fluka companies. All yields refer to isolated products. ^1H and ^{13}C NMR spectra were recorded on a Bruker (Rheinstetten, Germany) NMR spectrometer (at 500 and 400 MHz) using tetramethylsilane (TMS) as internal standard. Melting points were determined in a capillary tube. The progress of

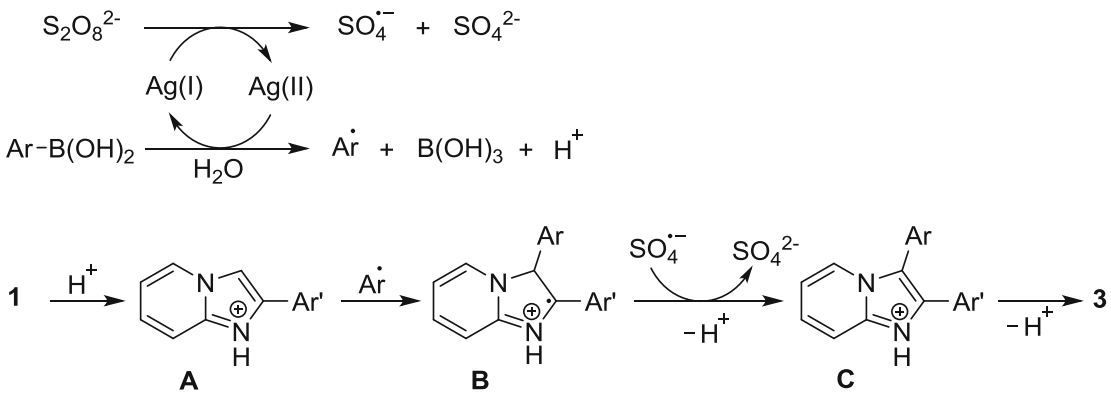
Table 2 The substrate scope of 2,3-diarylimidazo[1,2-*a*]pyridine derivatives (Scheme 1)

Entry	Prod	Ar′	Ar	M.p./°C	Lit. m.p./°C	Yield/%[a]
1	**3a**	Ph	Ph	150–152	149–150 [22]	71
2	**3b**	Ph	4-Me-Ph	134–136	136–137 [22]	73
3	**3c**	Ph	4-F-Ph	144–145	146–147 [28]	75
4	**3d**	Ph	4-NO_2-Ph	143–145	141–142 [22]	70
5	**3e**	Ph	4-Pyridyl	181–183	181–182 [22]	72
6	**3f**	Ph	3-Me-Ph	163–165	163–164 [28]	76
7	**3g**	4-MeO-Ph	Ph	102–105	101–102 [22]	79
8	**3h**	4-Cl-Ph	Ph	138–139	138–139 [28]	77

Reaction conditions: all reactions were performed with **1** (1 mmol), **2** (1.5 mmol), $AgNO_3$ (20 mol%), oxidant (3 eq.), TFA (1 eq.), 6 cm^3 CH_2Cl_2:H_2O (1:1), rt, 12 h

[a] Isolated yields

Scheme 2



the reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates. All products are known compounds and their structures were deduced by ^1H and ^{13}C NMR spectroscopies.

Typical procedure for the preparation of compounds 3a–3h

To a solution of imidazo[1,2-*a*] pyridine (1 mmol, 1equiv) in 3 cm^3 dichloromethane was added trifluoroacetic acid (1 mmol, 1 equiv) and arylboronic acid (1.5 mmol, 1.5 equiv). Water (2 cm^3) was then added, followed by silver(I) nitrate (0.2 mmol, 20 mol%) in 1 cm^3 water. Potassium persulfate (3 mmol, 3 equiv) was then added and the solution was stirred vigorously at room temperature and was screened by TLC. After completion of the reaction, the reaction mixture was diluted with 6 cm^3 dichloromethane and washed with 5% sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3 × 4 cm^3), dried over sodium sulfate, and evaporated in vacuum. Purification was performed by column chromatography using hexane:ethyl acetate (1:4) to obtain desired products.

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