Catalysis Communications 26 (2012) 11–14

Contents lists available at SciVerse ScienceDirect

Catalysis Communications

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

Short Communication

Highly regioselective C–H bond functionalization of imidazo[1,2-*a*]pyridines with aryl halides catalyzed by Ru-arene complex

Hai Yang [a,*], Liping Yang [b], Yuan Li [a], Fan Zhang [a], Huajie Liu [a], Bing Yi [a,*]

[a] College of Chemistry and Chemical Engineering, Hunan Institute of Engineering, Xiangtan 411104, PR China
[b] Department of Environmental Engineering, Xiamen University of Technology, Xiamen 361024, PR China

ARTICLE INFO

Article history:
Received 2 April 2012
Received in revised form 27 April 2012
Accepted 30 April 2012
Available online 11 May 2012

Keywords:
Imidazo[1,2-*a*]pyridine
Arylation
Ru-catalyzed
Coupling reaction

ABSTRACT

An effective Ru-catalyzed coupling reaction of imidazo[1,2-*a*]pyridines and aryl halides is reported for the synthesis of polysubstituted imidazo[1,2-*a*]pyridines through C–H bond cleavages. The current study presents a convenient strategy to synthesize polysubstituted imidazo[1,2-*a*]pyridine, a common structural motif in natural products and pharmaceuticals. Desired products in considerable yields can be obtained in the presences of $[RuCl_2(p\text{-cymene})]_2$ and Cs_2CO_3 in DMF at 120 °C after 15 h.

1. Introduction

Synthesis of polysubstituted imidazo[1,2-a]pyridines has received great attention because of their broad range of biological activities. Imidazo[1,2-a]pyridines have been prepared via the efficient C–H arylation of azole heteroarenes catalyzed by palladium complexes [1]. Later, the synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines was achieved through Suzuki cross-coupling reaction followed by a direct arylation [2]. Cao et al. also reported a convenient method for the copper(I)-catalyzed arylation of substituted imidazo[1,2-a]pyridines [3]. Morevoer, the imidazo[1,2-*a*]pyridine derivatives as important fine chemicals have been found to be key structural units in many natural products and drugs, such as alpidem, necopidem, saripidem, olprinone, zolpidem and zolimidine (Fig. 1), which are all commercially available [4,5]. Therefore, exploring new strategies to prepare imidazo[1,2-*a*]pyridine derivatives is still important in organic synthesis.

Transition-metal-catalyzed direct C–H functionalization represents a powerful strategy for the formation of heteroaromatic molecules via coupling of two different fragments [6–9]. Significant progress has been achieved for the direct formation of C–C bonds as biaryls via C–H activation using various proelectrophiles or pronucleophiles. The reactions were catalyzed by various transition-metal based complexes, such as Pd- [10,11], Cu- [12–14], Ni- [15–17], Co- [18–20], Mn- [21,22], Fe- [23–25], Rh [26–29], or/and Ru [30,31] system. Among transition-metal-catalyzed cross-coupling reactions, Pd, Rh, and Ru are the most versatile and widely used metals for the direct arylation to synthesize diaryl compounds [30–32].

In order to explore an efficient catalytic activation system for the synthesis of polysubstituted imidazo[1,2-*a*]pyridine derivatives via arylation reaction, we herein report a highly versatile Ru-catalyzed coupling reaction of imidazo[1,2-*a*]pyridines and aryl halides for the formation polysubstituted imidazo[1,2-*a*]pyridine derivatives as shown in Scheme 1. This synthetic approach involves the formation of intermolecular aryl-aryl bond by Ru-mediated arylation of imidazo[1,2-*a*]pyridine with aryl halides in the presences of a suitable ligand and an inorganic base. And this strategy also addresses issues of synthetic efficiency, in the case of the regioselective Ru-catalyzed C-3 arylation reaction.

2. Experimental

Typical experimental procedure for the synthesis of **3a**: All reactions were performed under air atmosphere in a round bottom flask equipped with a magnetic stir bar. $[RuCl_2(p\text{-cymene})]_2$ (0.05 equiv), Cs_2CO_3 (2 equiv), **1a** (1 equiv), **2a** (1.2 equiv) and 3 mL DMF were added successively. The mixture was stirred at 120 °C for 15 h. After the reaction (monitored by TLC), water (10 mL) was then added. The solution was extracted with ethyl acetate (3 × 15 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was then removed, and the residue was separated by column chromatography to yield the pure sample **3a**.

^1H NMR spectra and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer and referenced to 7.26 ppm and 77.0 ppm for chloroform solvent respectively with TMS as internal standard. Mass spectra were recorded on a Shimadzu

* Corresponding authors. Tel.: +86 731 58680049; fax: +86 731 58680125.
E-mail addresses: yanghai1001@163.com (H. Yang), bingyi2004@126.com (B. Yi).

1566-7367/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.catcom.2012.04.032

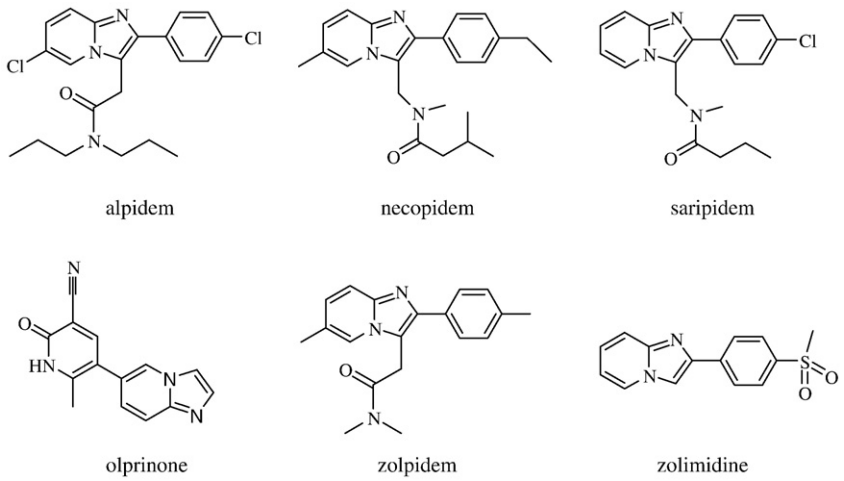


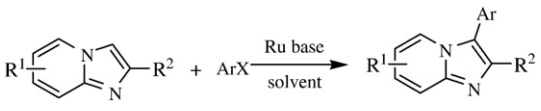
Fig. 1. Model drug structures containing imidazo[1, 2-a]pyridine.

GCMS–QP5050A at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF254), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

3. Results and discussion

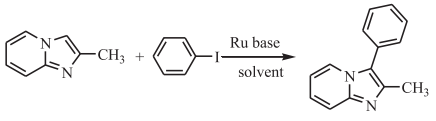
The potential catalysts and suitable reaction conditions were screened using the substrates of 2-methyl-imidazo[1,2-*a*]pyridine **1a** and iodobenzene **2a** for arylation reaction (Table 1). Firstly, the coupling reaction does not take place between **1a** and **2a** without ruthenium precursor (Table 1, entry 1). The effect of Ru source was then investigated. Interestingly, $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) shows the highest activity to give arylation product **3a** in good yield under the following condition: DMF (3.0 mL), 15 h, 120 °C, **1a** (0.5 mmol), **2a** (0.6 mmol), Ru-catalyst (5 mol%), and K_2CO_3 (1.0 mmol) (Table 1, entry 6). However, relative lower activity was obtained when the other Ru-catalysts were applied, such as $Ru_3(CO)_{12}$, $RuCl_2(H_2O)_n$, $RuCl_2(PPh_3)_3$ and $Ru(acac)_2$ (Table 1, entries 2–5). Subsequently, by fixing $[RuCl_2(p\text{-cymene})]_2$ and K_2CO_3 as Ru-catalyst and inorganic base, the reaction was carried out in different solvents instead of DMF, such as toluene, dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP) and dimethyl acetamide (DMAc). Only 22–72% of the arylation product and the remaining starting materials can be isolated (Table 1, entries 7–10), indicating that DMF provides the best performance compared to the other solvents. Next, the effect of inorganic bases was also studied. Among various inorganic bases examined, Cs_2CO_3 is the most efficient. The catalytic efficiency of the inorganic bases can be arranged in a deceasing order as following: Cs_2CO_3, K_2CO_3, Na_2CO_3 $NaHCO_3$, KH_2PO_4 and KOAc (Table 1, entries 6, 11–15). No significant decrease of yields was found when the reaction was protected by N_2 atmosphere (Table 1, entry 12). Finally, the reaction temperature was also tested. It can be seen that the temperature of 120 °C is quite necessary and lower or higher temperature is not suitable for this transformation (Table 1, entries 16–18).

Under optimized conditions (Table 1, entry 12), we then explored the scope of the catalytic system for arylation reaction of substituted imidazo[1,2-*a*]pyridines with aryl halides. Firstly, by fixing 2-methyl-imidazo[1,2-*a*]pyridine (**1a**) as the substrate, we carried out the reactions with various types of aryl halides, such as PhX, *o*-MePhX, *m*-MePhX, *p*-MePhX, *o*-EtPhX, and *p*-CNPhX (Table 2, entries 1–6). The higher isolated yield can be achieved with the *para*-substitued aryl halide but the relatively lower with the *ortho*-substitued aryl halide as shown in entries 2–4. However, when we replaced the electron-donating group with a strong electron-withdrawing group like cyan (see entries 4 and 6), the yield decreased remarkably. The results indicate that electron-withdrawing substituted groups on aryl halides disfavor the reaction. Subsequently, the influence of different substituted groups on imidazo[1,2-a]pyridine ring was investigated. When we changed the substrate from 2-methyl-imidazo[1,2-*a*]pyridine (**1a**) to 2-(trifluoromethyl)-imidazo[1,2-*a*] pyridine (**1b**) by replacing the methyl group on C-2 position of the imidazole ring with an electron-withdrawing group 'trifluoromethyl' (Table 2, entries 7–10), the substrate of **1b** exhibited better performances than **1a** if using the same



Scheme 1. Ru-catalyzed arylation reaction.

Table 1
Condition screening for the Ru-catalyzed direct arylation reaction of **1a** with **2a**.

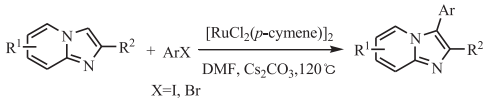


1a **2a** **3a**

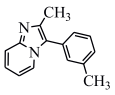
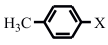
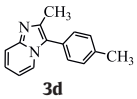
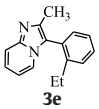
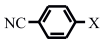
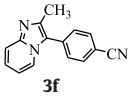
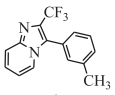
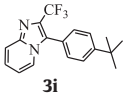
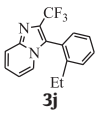
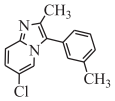
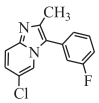
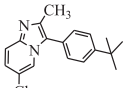
Entry	Catalyst (mol)[a]	Base	Solvent	T (°C)	Yield (%)[b]
1	No catalyst	K_2CO_3	DMF	120	–
2	$Ru_3(CO)_{12}$	K_2CO_3	DMF	120	43
3	$RuCl_2(H_2O)_n$	K_2CO_3	DMF	120	31
4	$RuCl_2(PPh_3)_3$	K_2CO_3	DMF	120	52
5	$Ru(acac)_2$	K_2CO_3	DMF	120	51
6	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	DMF	120	79
7	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	Toluene	Reflux	22
8	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	DMSO	120	61
9	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	NMP	120	72
10	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	DMAc	120	54
11	$[RuCl_2(p\text{-cymene})]_2$	Na_2CO_3	DMF	120	59
12	$[RuCl_2(p\text{-cymene})]_2$	Cs_2CO_3	DMF	120	86/85[c]
13	$[RuCl_2(p\text{-cymene})]_2$	$NaHCO_3$	DMF	120	33
14	$[RuCl_2(p\text{-cymene})]_2$	KH_2PO_4	DMF	120	21
15	$[RuCl_2(p\text{-cymene})]_2$	KOAc	DMF	120	19
16	$[RuCl_2(p\text{-cymene})]_2$	Cs_2CO_3	DMF	100	63
17	$[RuCl_2(p\text{-cymene})]_2$	Cs_2CO_3	DMF	140	41
18	$[RuCl_2(p\text{-cymene})]_2$	Cs_2CO_3	DMF	reflux	–

[a] Reaction condition: **1a** (0.5 mmol) and **2a** (0.6 mmol), Ru-catalyst (5 mol%), solvent (3 mL), 15 h.
[b] GC yield.
[c] Reaction under N_2 atmosphere.

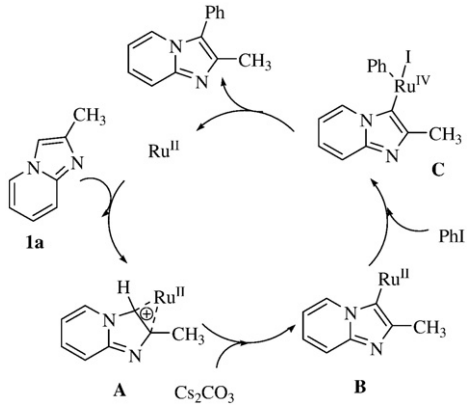
Table 2
Ru-catalyzed direct arylation of imidazo[1,2-*a*]pyridines with aryl halides.[a]



1a-c **2** **3a-m**

Entry	Substituted imidazo[1,2-*a*]pyridines	ArX	Products	Yield (%)[b]
1	**1a** $R^1=H$; $R^2=CH_3$		 **3a**	X = I, 84 X = Br, 74
2	**1a**		 **3b**	X = I, 80 X = Br, 70
3	**1a**		 **3c**	X = I, 89 X = Br, 71
4	**1a**		 **3d**	X = I, 93 X = Br, 86
5	**1a**		 **3e**	X = I, 84 X = Br, 72
6	**1a**		 **3f**	X = I, 81 X = Br, 70
7	**1b** $R^1=H$; $R^2=CF_3$		 **3g**	X = I, 90 X = Br, 77
8	**1b**		 **3h**	X = I, 90 X = Br, 82
9	**1b**		 **3i**	X = I, 92 X = Br, 85
10	**1b**		 **3j**	X = I, 86 X = Br, 75
11	**1c** $R^1=6$-Cl; $R^2=CH_3$		 **3k**	X = I, 87 X = Br, 71
12	**1c**		 **3l**	X = I, 80 X = Br, 71
13	**1c**		 **3m**	X = I, 84 X = Br, 77

[a] Reaction condition: **1** (1 equiv) and **2** (1.2 equiv), Ru-catalyst (5 mol%), solvent (3 mL), 15 h, 120 °C.
[b] Isolated yield.



Scheme 2. Proposed mechanism for Ru-catalyzed arylation.

aryl halides. The results show that electron-withdrawing substituted groups on the imidazole ring of the substrate actually favor the reactions. However, if the electron-withdrawing substituted group is on the pyridine ring by applying 6-chloro-2-methyl-imidazo[1,2-*a*]pyridine (**1c**) as the substrate (Table 2, entries 11–13), the chloro-group does not affect the isolated yield of arylation products obviously.

A proposed mechanism of the direct arylation of imidazo[1,2-*a*]pyridine **1a** with **2a** can be described in Scheme 2. The mechanism is consistent with previous studies on the arylation of heterocycles [33]. The first step is the C–H activation, and the reaction took place between **1a** and Ru(II) catalyst to form the unstable cationic three-member cycle intermediate **A**. Subsequently, abstraction of the acidic hydrogen atom in **A** with the help of Cs_2CO_3 would generate intermediate **B**, which possibly would then undergo aryl halides reversible oxidative addition to give the intermediate **C**. At last, intermediate **C** underwent reductive elimination to give the product **3a** and release the Ru(II) catalyst.

4. Conclusion

In summary, based on C–H activation, an efficient, direct Ru-catalyzed arylation method for the arylation of imidazo[1,2-*a*]pyridines with aryl halides was developed. The arylation exhibits high regioselectivity for imidazo[1,2-*a*]pyridines containing C-2 substituted group, and the arylation product of C-3 position could be isolated in moderate to excellent yields.

Acknowledgments

The authors gratefully acknowledge the generous financial support from National Natural Science Foundation of China (No. 21172064, 20972045), Provincial Natural Science Foundation of Hunan (No. 10JJ2006), the Key Scientific Research Fund of Hunan Provincial Education Department (No. 10A022), and the Starting Research Fund for Ph.D from Hunan Institute Engineering.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.04.032.

References

[1] B.B. Touré, B.S. Lane, D. Sames, Organic Letters 8 (2006) 1979–1982.
[2] S. Marhadour, M.A. Bazin, P. Marchand, Tetrahedron Letters 53 (2012) 297–300.
[3] H. Cao, H.Y. Zhan, Y.G. Lin, X.L. Lin, Z.D. Du, H.F. Jiang, Organic Letters 14 (2012) 1688–1691.
[4] A. Elhakmaoui, A. Gueiffier, J.C. Milhavet, Y. Blache, J.P. Chapat, O. Chavignon, J.C. Teulade, R. Snoeck, G. Andrei, E.D. Clercq, Bioorganic & Medicinal Chemistry Letters 4 (1994) 1937–1940.
[5] M. Andaloussi, E. Moreau, N. Masurier, J. Lacroix, R.C. Gaudreault, J.M. Chezal, A.E. Laghdach, D. Canitrot, E. Debiton, J.C. Teulade, O. Chavignon, European Journal of Medicinal Chemistry 43 (2008) 2505–2517.
[6] K. Godula, D. Sames, Science 312 (2006) 67–72.
[7] R.A. Altman, S.L. Buchwald, Nature Protocols 2 (2007) 2474–2479.
[8] J.S. Tian, T.P. Loh, Angewandte Chemie International Edition 49 (2010) 8417–8420.
[9] A. Renaudat, L. Jean-Gerard, R. Jazzar, C.E. Kefalidis, E. Clot, O. Baudoin, Angewandte Chemie International Edition 49 (2010) 7261–7265.
[10] M. Wasa, K.S.L. Chan, J.Q. Yu, Chemistry Letters 40 (2011) 1004–1006.
[11] Q. Liu, G. Li, H. Yi, P. Wu, J. Liu, A.W. Lei, Chemistry A European Journal 17 (2011) 2353–2357.
[12] S. Qiao, K. Xie, J.S. Qi, Chinese Journal of Chemistry 28 (2010) 1441–1443.
[13] W.H. Wang, C.D. Pan, F. Chen, J.A. Cheng, Chemical Communications 47 (2011) 3978–3980.
[14] H.T. Yang, C. Xi, Z.W. Miao, R.Y. Chen, European Journal of Organic Chemistry 18 (2011) 3353–3360.
[15] A. Joshi-Pangu, M. Ganesh, M.R. Biscoe, Organic Letters 13 (2011) 1218–1221.
[16] G.L. Xie, T.Y. Li, X.M. Qu, J.C. Mao, Journal of Molecular Catalysis A: Chemical 340 (2011) 48–52.
[17] N. Matsuyama, K. Hirano, T. Satoh, M. Miura, Organic Letters 11 (2009) 4156–4159.
[18] W. Liu, H. Cao, J. Xin, L.Q. Jin, A.W. Lei, Chemistry A European Journal 17 (2011) 3588–3592.
[19] B. Li, Z.H. Wu, Y.F. Gu, C.L. Sun, B.Q. Wang, Z.J. Shi, Angewandte Chemie International Edition 50 (2011) 1109–1113.
[20] Q.A. Chen, L. Ilies, E. Nakamura, Journal of the American Chemical Society 133 (2011) 428–429.
[21] G. Cahiez, O. Gager, F. Lecomte, Organic Letters 10 (2008) 5255–5256.
[22] Y. Kuninobu, D. Asanoma, K. Takai, Synlett 19 (2010) 2883–2886.
[23] P.P. Singh, S. Gudup, S. Ambala, U. Singh, S. Dadhwal, B. Singh, S.D. Sawant, R.A. Vishwakarma, Chemical Communications 47 (2011) 5852–5854.
[24] T.M. Niu, Y.H. Zhang, Tetrahedron Letters 51 (2010) 6847–6851.
[25] C.L. Sun, B.J. Li, Z.J. Shi, Chemical Reviews 111 (2011) 1293–1314.
[26] A.S. Tsai, M.E. Tauchert, R.G. Bergman, J.A. Ellman, Journal of the American Chemical Society 133 (2011) 1248–1250.
[27] T.J. Gong, B. Xiao, Z.J. Liu, J. Wan, J. Xu, D.F. Luo, Y. Fu, L. Liu, Organic Letters 13 (2011) 3235–3237.
[28] J. Bouffard, K. Itami, Topics in Current Chemistry 292 (2010) 231–280.
[29] H.J. Kim, M. Kim, S. Chang, Organic Letters 13 (2011) 2368–2371.
[30] Y. Na, S. Park, S.B. Han, H. Han, S. Ko, S. Chang, Journal of the American Chemical Society 126 (2004) 250–258.
[31] E.J. Farrington, J.M. Brown, C.F.J. Barnard, E. Rowsell, Angewandte Chemie International Edition 41 (2002) 169–171.
[32] B. Stefane, J. Fabris, F. Pozgan, European Journal of Organic Chemistry 18 (2011) 3474–3481.
[33] H. Cao, H. Zhan, D. Shen, H. Zhao, Y. Liu, Journal of Organometallic Chemistry 696 (2011) 3086–3090.