ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3763–3765

www.rsc.org/chemcomm

COMMUNICATION

Pd(II)-catalyzed direct C5-arylation of azole-4-carboxylates through double C–H bond cleavage†

Ziyuan Li, Ling Ma, Jinyi Xu, Lingyi Kong, Xiaoming Wu and Hequan Yao*

Received 5th January 2012, Accepted 20th February 2012
DOI: 10.1039/c2cc00081d

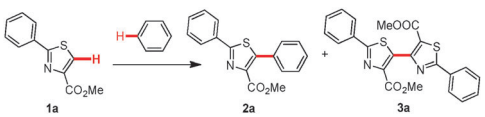
The first palladium-catalyzed direct C5-arylation of azole-4-carboxylates with simple unactivated arenes through double C–H bond cleavage is realized. This protocol provided a straightforward access to diverse 5-arylsubstituted azole-4-carboxylic derivatives with good functional group tolerance.

Azole moieties, such as thiazole and oxazole, are prevalent scaffolds found in a variety of natural products and pharmacophores, many of which possess interesting bioactivities.[1] For example, 5-arylated thiazole-4-carboxylic derivatives serve as good orexin receptor blockers for treating obesity[2] and 5-arylated oxazole-4-carboxylic derivatives are potent Cdc25 phosphatase antagonists as anticancer agents.[3]

To date, lots of efforts have been spent on developing practical methods for the transition-metal-catalyzed arylation of azoles at C2,[4] C4[5] and C5 positions.[6–15] Conventional C5 arylation of azoles relies on the use of stoichiometric organometallic compounds, such as $ArSnR_3$ and $ArB(OH)_2$, as nucleophilic components.[6,7] Recently, several groups[8–14] have independently reported pioneering palladium-catalyzed cross-coupling reactions to synthesize various 5-arylated azoles between aryl halides or arene tosylates/mesylates[15] and 5-unsubstituted azoles through single C–H bond cleavage. Although most of the above approaches could generate 5-arylated azoles in good yields, they required prefunctionalization of one or both of the coupling components. In the past several decades, transition-metal-catalyzed arylation of azoles has been extensively explored, however, to the best of our knowledge direct C5 arylation of azoles or azole-4-carboxylates with unactivated arenes through double C–H bond cleavage has never been reported so far. Over the past few years, significant breakthrough has been made in palladium(II)-catalyzed oxidative cross-couplings of unpreactivated heteroaryls and unactivated arenes through double C–H cleavage.[16,17] These methodologies represent an ideal strategy for the synthesis of biaryl compounds since they could avoid the need for preactivation of any coupling partner. During our continuing interest in the direct cross-coupling of azole-4-carboxylic derivatives at the 5-position, we observed that direct C5-arylation of methyl 2-benzylthiazole-4-carboxylate with *p*-xylene in DMF/DMSO with $Pd(OAc)_2$ could take place, albeit in fairly low yield.[18] In order to pursue a general procedure, we focused our interest on the direct C5 arylation of azole-4-carboxylates with simple unactivated arenes. We herein report our results.

Our initial investigation focused on the coupling of methyl 2-phenylthiazole-4-carboxylate (**1a**) with benzene as summarized in Table 1. Preliminary attempts using $Pd(OAc)_2$ as a catalyst and AgOAc as an oxidant in benzene at 80 °C led to the formation of the desired C5-arylated product **2a** in 44% yield, along with the homocoupled product **3a** in 38% yield (entry 1).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant (2 equiv.)	Additive (equiv.)	Yield[b] (%) (**2a/3a/1a**)
1[c]	$Pd(OAc)_2$	AgOAc		44/38/trace
2[d]	$Pd(OAc)_2$	AgOAc	—	59/27/trace
3	$Pd(OAc)_2$	AgOAc	DMSO[e]	21/67/0
4	$Pd(OAc)_2$	AgOAc	—	62/25/0
5	$Pd(OAc)_2$	Ag_2CO_3	—	46/39/7
6	$Pd(OAc)_2$	Ag_2O	—	Trace/92/0
7	$Pd(OAc)_2$	*p*-BQ	—	0/26/68
8	$Pd(OAc)_2$	$Cu(OAc)_2$	—	6/42/44
9	$Pd(OAc)_2$	IOAc	—	0/trace/56
10	$Pd(TFA)_2$	AgOAc	—	36/40/15
11	$PdCl_2(CH_3CN)_2$	AgOAc	—	54/16/12
12	$PdCl_2$	AgOAc	—	69/11/5
13	$PdCl_2$	AgOAc	K_2CO_3 (1)	0/82/5
14	$PdCl_2$	AgOAc	Cs_2CO_3 (1)	0/84/9
15	$PdCl_2$	AgOAc	KOAc (2)	0/35/53
16	$PdCl_2$	AgOAc	TFA (1)	38/19/33
17	$PdCl_2$	AgOAc	TsOH (1)	31/27/32
18	$PdCl_2$	AgOAc	AcOH (1)	66/18/6
19	$PdCl_2$	AgOAc	PivOH (1)	77/15/5
20	$PdCl_2$	AgOAc	PivOH (2)	79/13/6
21	$Pd(OAc)_2$	AgOAc	PivOH (2)	77/16/0

[a] Reaction conditions: methyl 2-phenylthiazole-4-carboxylate **1a** (0.5 mmol), Pd catalyst (0.05 mmol), oxidant (1 mmol) and additive in benzene (1.5 mL) at 120 °C for 12 h. [b] Isolated yields. [c] 80 °C. [d] 100 °C. [e] DMSO (0.15 mL).

State Key Laboratory of Natural Medicines and Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 210009, P. R. China. E-mail: hyao@cpu.edu.cn; Fax: +86 25-83301606; Tel: +86 25-83271042

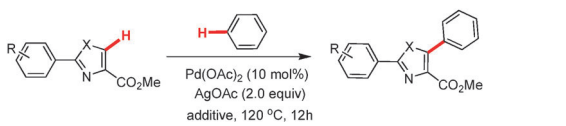
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of all title compounds. See DOI: 10.1039/c2cc00081d

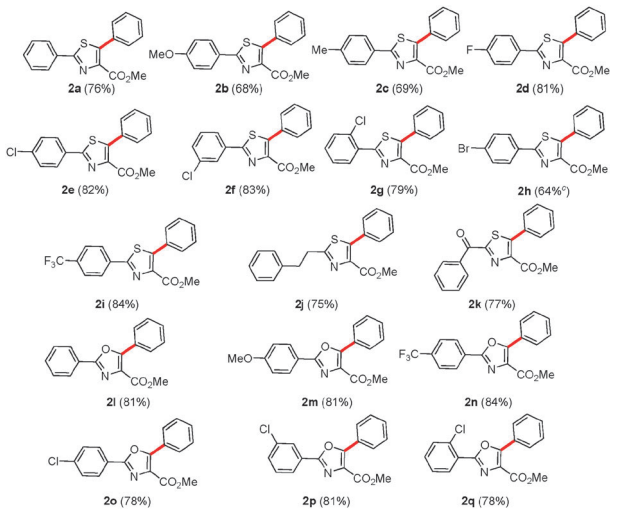
In the subsequent screening of reaction temperature, we found that the yield of **2a** was raised to 62% when the temperature was increased to 120 °C (entries 2–4). Very interestingly, most of **1a** was converted to **3a** when DMSO (10%, v/v) was used as co-solvent (entry 3), resulting in low yield of **2a**. Following the above results, we then performed the systematic screening on oxidants, catalysts, and additives. Oxidant screening showed that Ag_2CO_3 was less effective, whereas the use of Ag_2O or cheaper oxidants, such as *p*-BQ, $Cu(OAc)_2$ or IOAc, was entirely unsuccessful (entries 5–9). Catalyst screening revealed that $PdCl_2$ could give a similar result, while $Pd(CH_3CN)_2Cl_2$ or $Pd(TFA)_2$ was less effective (entries 10–12). Further screening using bases or acids as an additive (entry 13–21) indicated that PivOH (2 equiv.) exhibited good performance in reactivity.[19] Finally, we found that the combination of $Pd(OAc)_2$ and PivOH was the best system for fully consuming **1a** (entry 21), facilitating the purification of **2a** by flash chromatography.[20]

With the optimized conditions established, we first explored the effect of substituents at the C2 position on azoles (Table 2).[21,22] We were pleased to find that a range of substituents were tolerated under these conditions. For 2-phenyl-substituted thiazole substrates with electron-donating substitution on the phenyl ring, the reactions gave the desired products in moderate yields (**2b**, **2c**). On the other hand, the substrates with electron-withdrawing or halogen (F, Cl) substitutions on the phenyl ring could generate 5-arylated products in good yields (**2d–2i**). It is noteworthy that a 4-bromo-substituted substrate could also smoothly react with benzene to give the corresponding product **2h** in 64% yield when DMSO was used as an additive.[23] The tolerance of chloro and bromo substituents might provide an opportunity for further synthetic functionalization. In addition, 2-alkyl- or 2-carbonyl-substituted substrates could be arylated to achieve the desired cross-coupling products in moderate yields (**2j**, **2k**). Similarly to the thiazoles, all oxazole substrates could be smoothly converted to the corresponding products in good yields under the optimized conditions (**2l–2q**).

Next, the effective conditions were extended to a variety of unactivated arenes as illustrated in Table 3. Generally, the coupling preferentially occurred at the less sterically hindered position on arenes. For instance, when azoles coupled with toluene, it provided a mixture of 1,4- and 1,3-substituted products in moderate yields, and no 1,2-product was acquired (**4a**, **4b**). The good yields could be maintained when 1,2-disubstituted benzenes were used as an arene to couple with azoles (**4c–4h**). Most of these reactions furnished the 1,2,4-substituted product, along with no or a small amount of the 1,2,3-substituted isomer. With regard to more sterically hindered 1,3-disubstituted benzenes, the yields of the desired products slightly dropped and the 1,3,5-substituted product was found to be a major product (**4i**, **4j**). In contrast, the use of 1,4-disubstituted benzene as a simple arene for these arylations led to fairly poor yields of the desired arylated products (**4k**,**4l**) under the optimized conditions. To our delight, the coupling yields for *p*-xylene could be remarkably improved by substituting DMSO for PivOH as an additive (**4k**, **4l**) although the role of DMSO was not clear.[23] It should also be noted that electron-deficient benzene (nitrobenzene) could also couple

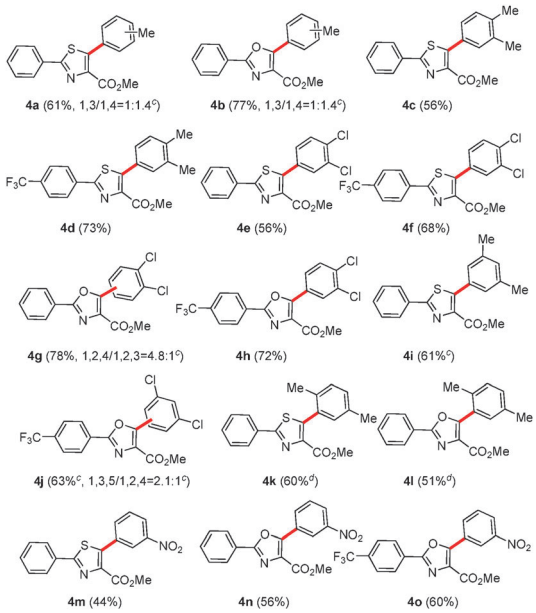
Table 2 Scope of azole-4-carboxylates[a,b]





[a] Reaction conditions: azole-4-carboxylate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), oxidant (1 mmol) and PivOH (1 mmol) in benzene (1.5 mL) at 120 °C for 12 h. [b] Isolated yield. [c] DMSO (0.15 mL) was used instead of PivOH at 100 °C for 12 h.

Table 3 Scope of unactivated arenes[a,b]



[a] Reaction conditions: azole-4-carboxylate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), oxidant (1 mmol) and PivOH (1 mmol) in arene (1.5 mL) at 120 °C for 12 h. [b] Isolated yield. [c] Determined by HPLC. [d] DMSO (0.15 mL) was used instead of PivOH.

with azoles to furnish 1,3-substituted products in acceptable yields (**4m–4o**).

To gain mechanistic insight of this process, we performed kinetic isotope effect studies (Scheme S2, ESI†).[24] By comparing the initial rates of benzene to those of benzene-d_6, the k_H/k_D values (by ^{1}H NMR) were determined to be 2.39 and 3.01 for thiazole and oxazole, respectively. The k_H/k_D values (by ^{1}H NMR) of H/D-azoles were determined to be 1.07 and 1.16 for thiazole and oxazole, respectively. The results suggest that the second C–H bond cleavage could be a rate-limiting step of the reaction. Thus, a plausible mechanism for the direct arylation of azoles is set out in Scheme S2 (ESI†).[24] This process is initiated by palladation of the azole at C5 to give palladium intermediate **A**. In the presence of an unactivated arene, the C5-palladated species **A** inserts slowly into the arene, and reductive elimination produces the arylated product, along with Pd(0) which is reoxidized by Ag(I) to complete the catalytic cycle.

In summary, we have developed the first Pd(II)-catalyzed direct C5-arylation of azole-4-carboxylates through double C–H bond cleavage with good functional group tolerance. This protocol provides a new avenue for synthesizing various 5-arylated azoles (Scheme S3, ESI†),[25] which could serve as useful building blocks for the synthesis of bioactive molecules. Preliminary studies of the reaction mechanism were also investigated. Detailed investigation on the reaction mechanism and application of this methodology to the synthesis of complex molecules are undertaken in our laboratory.

This research was supported by State Key Laboratory of Natural Medicines (JKGZ201110), NSFC-20902111, IRT1193 and Fundamental Research Funds for the Central Universities (2011BPY001 and JKY2011028 for ZL, JKZ2009002 for HY). We thank Haipin Zhou in this group for reproducing the results of **2i**, **2l** in Table 2, and **4d**, **4g** in Table 3.

Notes and references

1 (*a*) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 382; (*b*) A. C. Gaumont, M. Gulea and J. Levillain, *Chem. Rev.*, 2009, **109**, 1371.
2 (*a*) H. Aissaoui, C. Boss, R. Koberstein and T. Sifferlen, *PCT Int. Appl.*, WO 2009040730, 2009; (*b*) P. D. Coish, S. J. O'Connor, P. Wickens, C. Zhang and H. J. Zhang, *PCT Int. Appl.*, WO 2003037332, 2003.
3 A. P. Ducruet, R. L. Rice, K. Tamura, F. Yokokawa, S. Yokokawa, P. Wipf and J. S. Lazo, *Bioorg. Med. Chem.*, 2000, **8**, 1451.
4 For representative examples of C2-arylation of azoles, see (*a*) G. Huang, H. Sun, X. Qiu, C. Jin, C. Lin, Y. Shen, J. Jiang and L. Wang, *Org. Lett.*, 2011, **13**, 5224; (*b*) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.*, 2010, **132**, 1822; (*c*) F. Besselièvre, F. Mahuteau-Betzer, D. S. Grierson and S. Pigel, *J. Org. Chem.*, 2008, **73**, 3278; (*d*) F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2006, 1379.
5 For representative examples of direct C4-arylation of azoles, see (*a*) A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, 2003, **59**, 5685; (*b*) B. Liégault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826; (*c*) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 3276; (*d*) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer and K. Itami, *Angew. Chem., Int. Ed.*, 2011, **50**, 2387.
6 For excellent reviews, see: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*b*) J. Roger, A. I. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20.
7 For recent examples, see: (*a*) B. Liégault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047; (*b*) K. J. Hodgetts and M. T. Kershaw, *Org. Lett.*, 2003, **5**, 2911.
8 (*a*) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467; (*b*) A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, 2003, **59**, 5685.
9 Y. Kondo, T. Komine and T. Sakamoto, *Org. Lett.*, 2000, **2**, 3111.
10 (*a*) K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita and T. Iketa, *Org. Lett.*, 2004, **6**, 2011; (*b*) J. Shikuma, A. Mori, K. Masui, R. Matsuura, A. Sekiguchi, H. Ikegami, M. Kawamoto and T. Iketa, *Chem.–Asian J.*, 2007, **2**, 301.
11 M. Parisien, D. Valette and K. Fagnou, *J. Org. Chem.*, 2005, **70**, 7578.
12 G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2007, **46**, 7996.
13 J. Roger, F. Pozgan and H. Doucet, *J. Org. Chem.*, 2009, **74**, 1179.
14 C. Verrier, T. Martin, C. Hoarau and F. Marsias, *J. Org. Chem.*, 2008, **73**, 7383.
15 L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201.
16 For selected examples, see: (*a*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 11904; (*b*) B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1115; (*c*) G. Brasche, J. García-Fortanet and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 2207; (*d*) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172; (*e*) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072; (*f*) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef, *Org. Lett.*, 2007, **9**, 3137; (*g*) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254.
17 For excellent reviews on palladium-catalyzed aryl–aryl bond formation through double C–H activation, see: (*a*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*b*) S. L. You and J. B. Xia, *Top. Curr. Chem.*, 2010, **292**, 165; (*c*) J. A. Ashenhurst, *Chem. Soc. Rev.*, 2010, **39**, 540; (*d*) G. P. McGlacken and L. M. Batemann, *Chem. Soc. Rev.*, 2009, **38**, 2447; (*e*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*f*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2009, **109**, 1215.
18 (*a*) Z. Li, L. Ma, C. Tang, J. Xu, X. Wu and H. Yao, *Tetrahedron Lett.*, 2011, **52**, 5643; (*b*) Z. Li, Y. Wang, Y. Huang, C. Tang, J. Xu, X. Wu and H. Yao, *Tetrahedron*, 2011, **67**, 5550.
19 The addition of PivOH into the reaction system produced $Pd(OPiv)_2$, which was proposed to enable efficient C–H palladation. See recent reviews: (*a*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*b*) D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, 1118.
20 See ESI† for detailed optimization.
21 For the synthesis of azole-4-carboxylic derivatives, see (*a*) Y. Huang, H. Gan, S. Li, J. Xu, X. Wu and H. Yao, *Tetrahedron Lett.*, 2010, **51**, 1751; (*b*) Y. Huang, L. Ni, H. Gan, Y. He, J. Xu, X. Wu and H. Yao, *Tetrahedron*, 2011, **67**, 2066; (*c*) Y. Wang, Z. Li, Y. Huang, C. Tang, X. Wu, J. Xu and H. Yao, *Tetrahedron*, 2011, **67**, 7406.
22 The arylation of 4-alkyl or 4-hydrogen substituted azoles under the optimized conditions was proved to be inefficient, resulting in the formation of the corresponding homocoupling product in high yield.
23 See ESI† for details.
24 See ESI† for mechanism studies.
25 Facile derivation of 5-arylated azole-4-carboxylates demonstrated that our protocol was capable of being applied to the synthesis of diverse 5-arylated azole-based molecules. See ESI† for details.