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Efficient palladium(II)-catalyzed homocoupling of thiazole-4-carboxylic or oxazole-4-carboxylic derivatives

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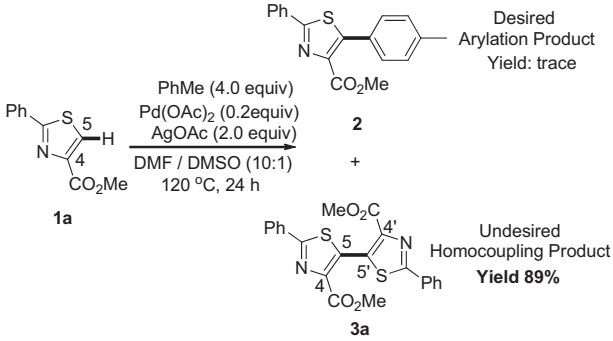
ABSTRACT

An efficient $Pd(OAc)_2$-catalyzed homocoupling of thiazole-4-carboxylic or oxazole-4-carboxylic derivatives is described. It represents a facile and practical methodology to prepare bis-5,5′-thiazole (oxazole)-4,4′-dicarboxylic derivatives in good to excellent yields. This protocol tolerates a series of substitutions on the thiazole (oxazole) rings, including alkyl, carbonyl, and electron-withdrawing/donating group substituted phenyl groups.

1. Introduction

Over past decades, significant progress has been achieved in transition-metal-catalyzed C–C bond formation where one or both of the carbon atoms are required to be pre-activated, such as the Mizoroki–Heck, Kumada, Stille, Negishi, Suzuki–Miyaura, Hiyama coupling, and Tsuji–Trost allylation.[1] More recently, direct conversion[2] of C–H bond to C–C bond via palladium (II) catalysis has been becoming an exceedingly valuable process in contemporary organic synthesis, allowing concise, economical, and environmental-benign routes to be applied to the synthesis of many useful functional chemicals or organic compounds with biological activities.

In light of the advances in this area, our interest in the synthesis of the biologically leads, such as new CDC25 inhibitors, inspired us to explore a general protocol for the direct 5-arylation of thiazoles.[3,4] When we treated methyl 2-phenylthiazole-4-carboxylate (**1a**) with 4 equiv of anhydrous toluene in DMF/DMSO using $Pd(OAc)_2$ as a catalyst (Scheme 1), however, only trace amount of the desired 5-aryl substituted product **2** was observed, and a homocoupling byproduct **3a** was acquired in very good yield. Encouraged by the promising result, we then turned our attention to this homocoupling reaction. As we know, many natural or synthetic compounds bearing the scaffold of bis-5,5′-thiazole or bis-5,5′-oxazole have been reported to have miscellaneous pharmaceutical applications or to be used as functional materials.[5]



Scheme 1. Palladium catalyzed homocoupling of thiazole-4-carboxylate.

Previous methods to implement the preparation of bis-5,5′-azoles usually required participation of halogen atoms,[6] which makes this conversion not economical and environmental-benign. Oxidative cross-coupling was also reported as an efficient method to achieve bis-5,5′-azoles, in which a strong base like *n*-BuLi was usually used to dissociate the hydrogen atom on the coupling site before the cross-coupling takes place.[5b,7] Recently, Mori and co-workers provided an example of the homocoupling of 2-(*p*-methoxyl)phenylthiazole

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using a $PdCl_2$(dppb)/AgOAc catalytic system when they focused on the homocoupling of thiophenes.[8] In addition, other examples of Pd(II)-catalyzed homocoupling of heteroarene have also been reported in the literatures.[9] Although various approaches have been developed for the preparation of bis-5,5′-azoles so far, no general catalytic system was reported for the homocoupling of thiazole-4-carboxylic or oxazole-4-carboxylic derivatives. Herein, we wish to describe a general reaction system for the homocoupling of various thiazole (oxazole)-4-carboxylic derivatives with wide compatibility via $Pd(OAc)_2$ catalyzed C–H bond activation.

2. Results and discussion

We began our investigation using **1a** as the model substrate. The results were summarized in Table 1. An initial attempt under a similar condition to that in Scheme 1 without toluene was successful within a remarkably shorter time even when a smaller catalyst loading (0.1 equiv) was tried (entry 1). Further attempts to evaluate reaction temperature and different combinations of catalysts and oxidants provided no better results (entries 2–9). Lower loading of $Pd(OAc)_2$ resulted in poorer yields of the desired product **3a** (entries 10 and 11). Replacing the metal oxidants with more cost-effective oxidants, such as BQ and O_2 were also detrimental to the yield (entries 12–18). Reactions without any palladium (II) catalyst provided no or only trace amount of **3a** (entries 19–21) suggesting the plausible mechanism of this conversion as illustrated in Fig. 1.[8] Electrophilic C–H substitution of Pd(II) catalyst with **1**, followed by disproportionation gives bis-thiazolepalladium species **B**. **B** undergoes a reductive elimination to afford the homocoupling product **3**. The Pd(II) catalyst is regenerated via an oxidation of Pd(0) to complete the catalytic cycle.

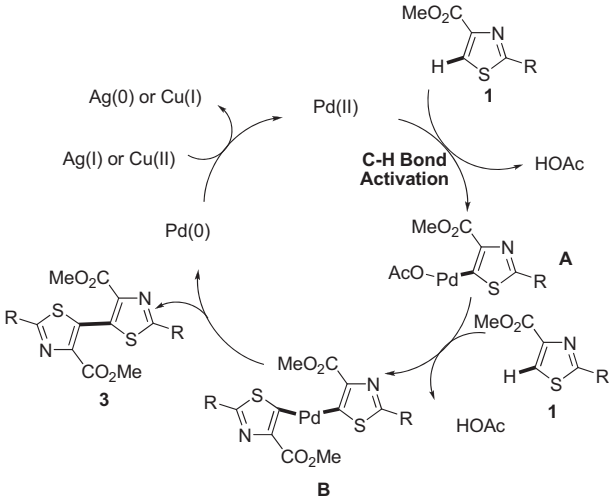
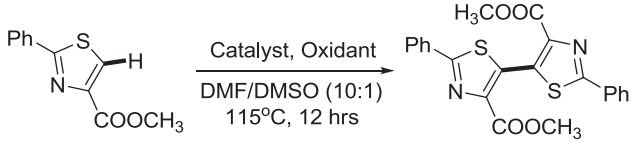


Fig. 1. Plausible mechanism of $Pd(OAc)_2$-catalyzed homocoupling.

Table 1
The screening of the reaction conditions[a]



1a 3a

Entry	Catalyst	Oxidant	**3a** (**1a**) (%)[b]
1	$Pd(OAc)_2$	AgOAc	91
2	$Pd(OAc)_2$	Ag_2CO_3	74
3	$Pd(OAc)_2$	$Cu(OAc)_2$	26(67)
4	$PdCl_2$	AgOAc	88
5	$PdCl_2$	Ag_2CO_3	40(51)
6	$PdCl_2$	$Cu(OAc)_2$	82(7)
7[c]	$Pd(OAc)_2$	AgOAc	84(8)
8[d]	$Pd(OAc)_2$	AgOAc	62(31)
9[e]	$Pd(OAc)_2$	AgOAc	31(67)
10[f]	$Pd(OAc)_2$	AgOAc	77(17)
11[g]	$Pd(OAc)_2$	AgOAc	27(66)
12	$Pd(OAc)_2$	BQ	47(47)
13	$Pd(OAc)_2$	O_2	21(68)
14	$PdCl_2$	O_2	trace
15[h]	$Pd(OAc)_2$	$AgOAc/O_2$	32(64)
16[h]	$PdCl_2$	$AgOAc/O_2$	17(75)
17[h]	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	68(21)
18[h]	$PdCl_2$	$Cu(OAc)_2/O_2$	24(58)
19	None	AgOAc	0
20	None	$CuCl_2$	0
21	None	$Cu(OAc)_2$	Trace

[a] Reaction conditions unless otherwise specified: **1a** (0.5 mmol), Pd(II) catalyst (0.05 mmol, 0.1 equiv), and oxidant (1.0 mmol, 2.0 equiv) in 1.5 ml DMF and 0.15 ml DMSO.
[b] Isolated yield.
[c] Conducted at 100 °C.
[d] Conducted at 80 °C.
[e] Conducted at 60 °C.
[f] $Pd(OAc)_2$ (0.05 equiv) was used.
[g] $Pd(OAc)_2$ (0.01 equiv) was used.
[h] AgOAc or $Cu(OAc)_2$ (0.1 equiv) was used as a co-oxidant besides O_2.

With the established condition in hand, we embarked on the investigation of the substrate scope. Compatibility of the established condition on various thiazole-4-carboxylic substrates was first examined, and the results were summarized in Table 2. All thiazole-4-carboxylate substrates were completely consumed within 12 h, and the homocoupling proceeded smoothly to give the corresponding products in good to excellent yields (**3a**–**p**). For those 2-substituted phenylthiazole-4-carboxylate substrates, the electronic property of the group on the benzene ring had some influences on the homocoupling reaction (**3a**–**j**, **3n**–**p**). Generally, strong electron-donating group substituted substrates provided the desired products in relatively lower yields (**3b** and **3d**). On the contrary, substrates with strong electron-withdrawing group or halogen atom on the benzene ring afforded the homocoupling products in higher yields (**3e**–**j**, **3o**, and **3p**), and much less adverse products were observed. This substitution effect on thiazoles could be explained by the fact that the Pd induced C–H bond activation process might be originated from the C–H acidity at 5-position of thiazoles.[8] Good results were also achieved for the substrates with akyl or benzoyl groups (**3k**–**m**). Although prolonged reaction time was required for the thiazole-4-formamide substrates to be fully consumed under this condition, but all provided the homocoupling products (**3q**–**u**) in good yields after 36 h. It is noteworthy that the homocoupling of a 2-monosubstituted substrate favored at the relatively electrophile-susceptible 5-position to afford the bis-5,5′-thiazole (**3v**) in excellent yield under the optimized condition.[6a]

Applications of the established protocol to the homocoupling of oxazole-4-carboxylic derivatives were also explored and the results showed similar patterns comparing to the thiazole substrates (Table 3). The homocoupling of all carboxylate substrates proceeded smoothly to afford the desired products in moderate to good yields within 12 h (**5a**–**g**). Among them, the yields of the homocoupling of 2-phenyloxazole-4-carboxylates with halo or electron-withdrawing group substitution on phenyl group were remarkably higher than that of other types of substitution, same as the thiazole substrates. Small amount of the oxazole-4-formamide substrates remained unconsumed even after a prolonged reaction time (36 h), resulting in relatively lower yields (**5h** and **5i**). To the