Research Article

FACILE SYNTHESIS OF 2,4-DISUBSTITUTED OXAZOLES VIA PALLADIUM/COPPER CO-MEDIATED DIRECT ARYLATION REACTION

Bhima Sridevi *

Department of Pharmaceutical Chemistry, Bharat Institute of Technology- Pharmacy, Hyderabad-501506, Telangana, India.

ABSTRACT

An efficient one step protocol is developed for the straight arylation of oxazoles with aryl halides using palladium-copper. The protocol provides quick access for the site-selective C-H arylations under mild reaction conditions which may be useful for the synthesis of analogues of alkaloid natural products balsoxin and texamine. Because of readily accessible substrates, simple operation, and high bioactivity of oxazoles, this strategy is a valuable addition for the synthesis of medicinally active agents.

Key words: Oxazoles, Arylation, Natural products, co-catalytic system.

INTRODUCTION

Oxazoles represent an important class of heterocyclic compounds due to their occurrence in natural product chemistry, medicinal chemistry and materials science.[1] Many approachs for the synthesis of such molecules have emerged, involving the building of the oxazole ring by nontrivial multistep reaction sequences. Since some of the oxazole derivatives have shown wide spread applications in medicinal chemistry,[2] much effort has been focussed towards devising methods for the synthesis of substituted oxazoles.[3]Among the oxazole-type compounds, benzoxazoles and 2-phenyloxazoles are the most frequently encountered substrates.[4]

Some representative examples of oxazoles containing natural products are shown in Figure 1.

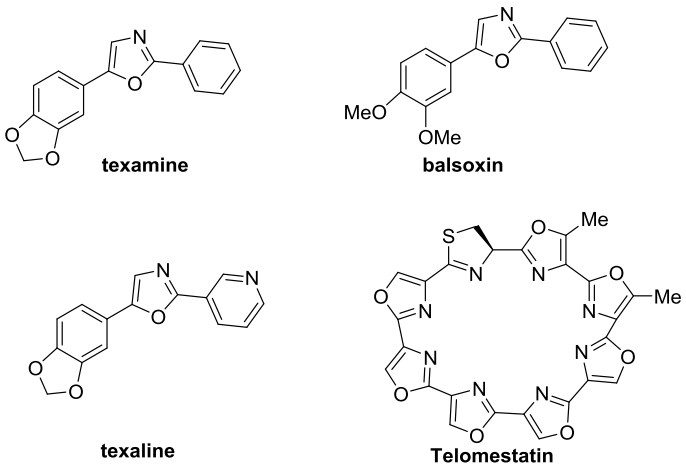


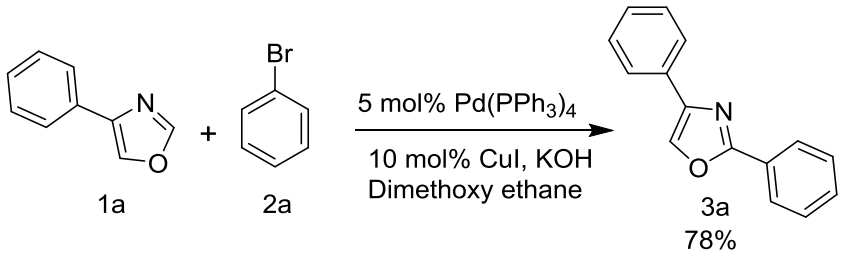
Fig. 1: Biologically active natural products

Due to the pharmaceutical importance, various synthetic methods have been developed for the concise and efficient synthesis of highly substituted oxazole structures.[5,6] Hoarau et al.[7] have described a regioselective palladium-catalyzed C-2 arylation of electron poor substituent like ethyl 4-oxazole-carboxylate with iodobenzene. Similarly, Li et al.[8] have reported the C-2 arylation of methyl 4-aryl-5-oxazole carboxylate with aryl iodides employing copper. Later, Deng et al. have reported the arylation of azoles, and indoles using $ArSO_2Na$ and $ArSO_2Cl$.[9] Recently, Tamagnan et al. have further reported the first example of Pd(0)/Cu(I)- catalyzed direct arylation of benzoxazole.[10] In addition, Miura et al. developed Ni(II)-catalyzed direct arylation of benzoxazoles and oxazoles with arylboronic acids under aerobic conditions.[11] All these literature mentioned revealed that most of the methods suffered from regioselectivity and poor yields with tedious synthetic procedures.[12]

Recently, the C−H bond activation using transition-metal catalysis have received much interest and constitutes one of the most significant aspect in modern organic chemistry.[13] In this regard, various metals such as Rh,[14a] Ru,[14b] Fe,[14c] Cu,[14d] Ag,[14e] and Pd[14f] have made remarkable contributions. Although numerous reports available for C−H activation, however fewer methods only accessible for direct arylations at the position-2 of monosubstituted oxazoles with aryl halides are much less documented. In this context, it is desirable to develop the direct metal-catalyzed arylation of 4-substituted oxazoles with inexpensive and readily available aryl bromides.

RESULTS AND DISCUSSION

With the extensive interest in the area of C-H activation and bioactivity of oxazoles, we were intended to report Pd(0)/Cu(I) catalysed C-2 arylation of 4-substituted oxazoles.



Scheme 1. Synthesis of 2,4-diphenyloxazole (3a).

On the set, a model reaction was attempted for the coupling of 4-phenyloxazole **1a** with bromo benzene was primarily studied. Compound **1a** was readily prepared from phenacyl bromide in one step in 75% yield.[15] A reaction was performed using oxazole (**1a**) and bromo benzene (**2a**) in the presence of Pd(0) (5 mol%) as catalyst and the product was observed in trace amount only. Next, $Cu(OAc)_2$ (10 mol%) was used as a co-catalyst, KOH (1 equiv.) as base and the product observed in moderate yield (45%, entry **4,** Table 1). Under these conditions, other protic and aprotic solvents were examined and proved less favorable. Further the effect of co-catalyst on product yield has studied under similar conditions various copper catalysts such as $Cu(OTf)_2$, Cu(OTf), CuCl and CuI. Among them, CuI (10 mol%) displayed the best results in terms of conversion (entry 2, Table 1). The yield was improved from 45% to 78% when 10mol%. of CuI was used (entry 2, Table 1). Therefore, $Pd(PPh_3)_4$ (5 mol %), CuI (1 equiv.), and KOH (1 equiv.) in DME at 120 °C was found to be the optimal conditions for this protocol.

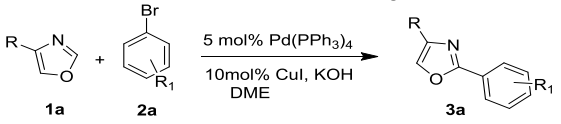
Table 1: Screening the co-catalysts in the formation of 3a[a]

entry	co-catalyst	mol%	solvent	Time (h)	Yield (%)[b]
1	CuI	5	DME	6	55
2	CuI	10	"	"	78
3	CuI	15	"	"	76
4	$Cu(OAc)_2$	10	"	"	45
5	CuOTf	10	"	"	40
6	$Cu(OTf)_2$	10	"	"	35
7	CuCl	10	"	"	60

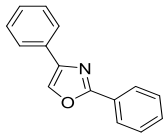
[a]Reaction was performed at 0.5 mmol scale with respect to oxazole
[b]yield refers to pure product after column chromatography

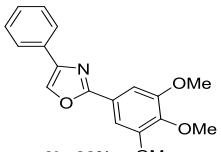
With these optimized reaction conditions in hand various aromatic aryl halides such as 3,4,5-trimethoxy bromo benzene, 4-methyl benzene, 3,4-dimethoxy bromo benzene and 3-methyl bromo benzene was employed. In all cases, the corresponding 2,4-disubstituted oxazole derivatives were obtained in good yields (Table **2**). Next, we have examined the electronic factors of different 4-aryl substituted oxazoles, interestingly we have observed high yields with electron withdrawing groups(**3b** and **3e**) . In addition, this method works not only with aromatic oxazoles but also with aliphatic oxazoles. In case of aliphatic oxazoles, the corresponding 2,4-alkyl substituted oxazoles were obtained in slightly lower yields (entries **3g**, **3h**, **3i** and **3j**, Table **2**) than aromatic counterpart. In all the cases, the reactions proceeded efficiently in the presence of 5 mol% $Pd(PPh_3)_4$, 1eq. CuI and 1eq. KOH at 120°C in Dimethoxy ethane, and the corresponding products were obtained in good yields.

Table 2: Reaction with various aryl bromides

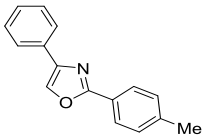


1a 2a 3a

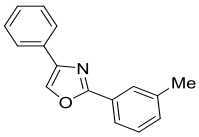

3a, 78%



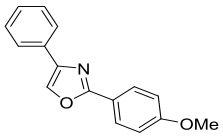
3b, 82%



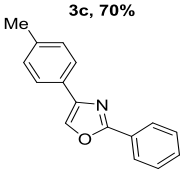
3c, 70%



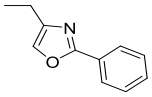
3d, 73%

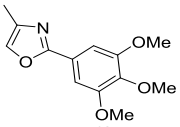


3e, 79%

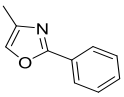


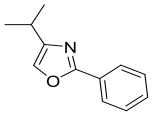
3f, 69%


3g, 62%



3h, 65%

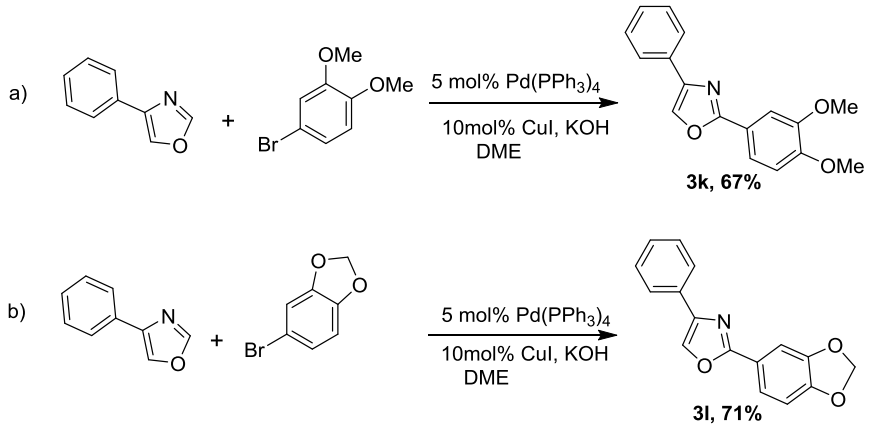

3i, 58%


3j, 60%

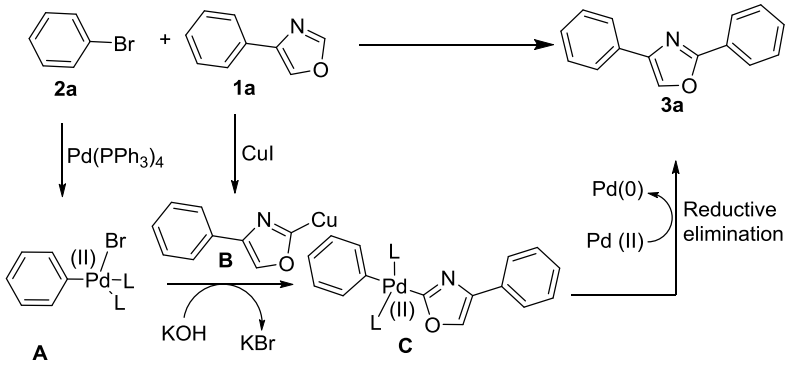
[a] Reaction condition: 4-substituted oxazole 1(1 mmol), aryl halide 2 (1 mmol), $Pd(PPh_3)_4$ (5 mol%) CuI (10mol%), KOH (1 mmol), DME, 120 °C.
[b] Isolated yields.

To show the synthetic utility, we applied the present protocol for the synthesis of two oxazole natural products balsoxin and texamine. The 2,4- diaryloxazole motif is originate in a variety of natural products such as texamine and balsoxin (Figure 1), which were isolated from the roots of *Amyris texana* and *A. Plumier* respectively. Here we synthesized 2,4- diaryloxazole analogues of texamine and balsoxin in one step from commercially available starting materials (Scheme 2). This procedure is efficient and practical compared to previous methods.

Scheme 2: Synthesis of texamine and balsoxin analogues 3k and 3l.



On the basis of these results, a mechanism is proposed (Scheme 3). It is assumed that intially, the Pd catalyst may react with bromo compound **2a** to form a Pd(II) species **A**. Which then, reacts with the oxazolyl copper intermediate **B** that was generated from oxazole **1a** in the presence of CuI, leading to formation of a transmetallated aryl heteroaryl palladium(II) complex **C**. Reductive elimination of which furnishes the required product **3a**.



Scheme 3: Plausible mechanism

CONCLUSION

We have developed a highly versatile and straightforward protocol for the synthesis of 2,4-di substituted oxazoles using $Pd(PPh_3)_4$ and CuI co-catalytic system direct arylation of 4-aryl/alkyl oxazoles with various aryl bromides. The potentiality of this protocol was associated with a wide board substrate scope and simple reaction procedure with mild reaction conditions. The high functional group tolerance and the speed of the reaction afford this method appropriate for the combinatorial synthesis of a variety of 2,4-di substituted oxazoles. Moreover, this protocol can be used as an alternative method to the harsh traditional existing methods.

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