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Research Article

HIGHLY EFFICIENT SYNTHESIS OF 2,4-DISUBSTITUTED OXAZOLES THROUGH PALLADIUM/COPPER COMEDIATED DIRECT ARYLATION REACTION

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ABSTRACT

Objective: The aim of the present study is to synthesize 2,4-disubstituted oxazoles through palladium/copper comediated direct arylation reaction.

Methods: 2,4-disubstituted oxazoles (3a-i) have been synthesized by the reaction of 4-substituted oxazole with aryl bromide in the presence of KOH , CuI and Pd(PPh3)4 in dimethoxyethane. Titled compounds (3a-i) were obtained in good yields using an expedient two-step synthesis of 2,4-disubstituted oxazoles from commercially available starting materials

Results: The structures of the newly synthesized compounds were characterized by Fourier-transform infrared, 1H NMR, 13C NMR, and mass spectral studies. This method can be an efficient method for the synthesis of 2,4-disubstituted oxazoles (3a-i).

Conclusion: Pd(PPh3)4 and CuI cocatalytic system direct arylation of 4-aryl/alkyl oxazoles with various aryl bromides has been developed to generate 2,4-disubstituted oxazoles. 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-disubstituted oxazoles.

Keywords: Oxazoles, Arylation, Palladium/copper.

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INTRODUCTION

Oxazoles are one of the common substructures in a wide variety of biologically active compounds, synthetic intermediates, and pharmaceuticals [1]. Many approaches for the synthesis of such molecules have emerged, involving the building of the oxazole ring by nontrivial multistep reaction sequences. Since oxazole derivatives have wide spread applications in medicinal chemistry [2]. Much effort has been focused toward devising methods for the synthesis of substituted oxazoles [3]. The activation of a C–H bond by transition-metal catalysis has received increasing interest recently and constitutes one of the most significant fields of modern organic chemistry [4]. In this regard, various metals, such as Rh,[5a] Ru,[5b] Fe,[5c] Cu,[5d] Ag,[5e] and Pd,[5f] have made remarkable contributions[5]. However, much less work has been reported for the preparation of oxygen-containing heterocycles through palladium catalyzed C–H activation.

Among the oxazole-type compounds, benzoxazoles and 2-phenyloxazoles are the most frequently encountered substrates [6]. Therefore, various synthetic methods have been developed for the concise and efficient synthesis of highly substituted oxazole structures [7,8]. Direct arylations at the 2-position of monosubstituted oxazoles with aryl halides are much less well documented. Hoarau *et al*. have described a regioselective palladium-catalyzed C-2 arylation of ethyl 4-oxazolecarboxylate with iodobenzene, while Li *et al*. have reported the C-2 arylation of methyl 4-aryl-5-oxazole carboxylate with aryl iodides under classical conditions in the presence of copper(I) iodide [9,10]. Li J *et al*. have recently reported the arylation of azoles, and indoles using ArSO2Na and ArSO2Cl [11]. In recently, Tamagnan further reported the first example of Pd(0)/Cu(I)-catalyzed direct arylation of benzoxazole [12]. In addition, Hachiya *et al*. developed Ni(II)-catalyzed direct arylation of benzoxazoles and oxazoles with arylboronic acids under oxygen [13]. In this context, a study of the direct metal-catalyzed arylation of 4-substituted oxazoles with aryl bromides, being together cheaper and more broadly available than the corresponding iodides, was undertaken.

METHODS

We herein report a simple and convenient approach for the synthesis of 2,4-disubstituted oxazoles through the arylation of 4-substituted oxazole in a single step. As a model reaction, the coupling of 4-phenyloxazole 1a with bromobenzene was primarily studied. Compound 1a was readily prepared from phenacyl bromide in one step in 75% yield [14]. We initiated our studies with the screening of the conditions for the coupling of oxazole (1a) and bromobenzene (2a) under palladium catalysis. Initially, when $Pd(PPh3)_4$ (5 mol%) was selected as the catalyst and $Cu(OAc)_2$ (1 equiv.) was used as an oxidant in dimethoxyethane in the presence of 1 equiv. of KOH base, the coupled product was obtained in 45% yield (Table 1, Entry e). Under these conditions, other protic and aprotic solvents examined proved less favorable. The efficiency was further affected by an oxidant. The yield was improved from 45% to 78% when 1 equiv. of CuI was applied (Table 1, Entry b). To optimize the reaction conditions, several copper catalysts such as $Cu(OTf)_2$, Cu(OTf), CuCl, and CuI were screened. Among them, 1 eq. of CuI gave the best results in terms of conversion (Fig. 2). Next, we studied the effect of solvent. Of various solvents, dimethoxyethane was found to be effective resulting in the formation of 3a in high yields. Therefore, optimal conditions for reaction were Pd(PPh3)4 (5 mol %), CuI (1 equiv.), and KOH (1 equiv.) in dimethoxyethane (DME) at 120°C.

Next, we extended this method to other aromatic aryl halides such as 3,4,5-trimethoxy bromobenzene, 4-methyl benzene, 3,4-dimthoxy bromobenzene, and 3-methyl bromobenzene. In all cases, the corresponding 2,4-disubstituted oxazole derivatives were obtained in good yields (Entries b, c, and d, Fig. 3). Next, we examined the reactivity of different 4-aryl-substituted oxazoles; interestingly, we are observed good yields (Entry f, Fig. 3). In addition, this method works not only

Table 1: Screening the cocatalysts in the formation of 3a[a]

Entry	Co-Catalyst	Equiv.	Solvent	Time (h)	Yield (%)[b]
a	CuI	0.5	DME	6	55
b	CuI	1	”	”	78
c	CuI	1.5	”	”	63
d	CuI	2	”	”	60
e	Cu $(OAc)_2$	1	”	”	45
f	CuOTf	1	”	”	40
g	Cu $(OTf)_2$	1	”	”	35
h	CuCl	1	”	”	60

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

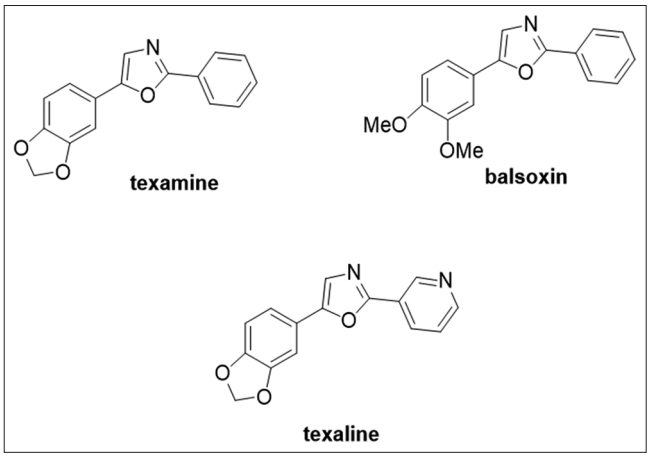

Fig. 1: Biologically active natural products

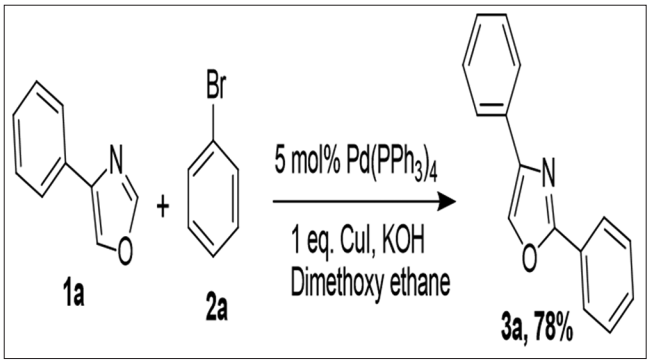

Fig. 2: Synthesis of 2,4-diphenyloxazole (3a)

with aromatic oxazoles but also with aliphatic oxazoles. In case of aliphatic oxazoles, the corresponding 2,4-alkyl-substituted oxazoles were obtained relatively in lower yields (Entries g, h, I, and j, Fig. 3) than aromatic counterpart. In all the cases, the reactions proceeded efficiently in the presence of 5 mol% $Pd(PPh3)_4$, 1 eq. CuI, and 1 eq. KOH at 120°C in dimethoxyethane, and the corresponding products were obtained in good yields.

To show the synthetic utility, we applied the present protocol to the synthesis of an analog of balsoxin and texamine. The 2,5-diaryloxazole motif is originate in a variety of natural products such as texamine and balsoxin (Fig. 1), which were isolated from the roots of *Amyris texana* and *Amyris plumieri*, respectively. Here, we synthesized 2,4-diaryloxazole analogs of texamine and balsoxin in one step from commercially available starting materials (Fig. 4). This procedure is efficient and practical compared to previous methods.

RESULTS AND DISCUSSION

1H and 13C nuclear magnetic resonance (NMR) spectra were recorded on BrukerAvance500 MHz, 300 MHz, and ^{13}C NMR at 125 MHz, 75 MHz. For ^{1}H NMR, tetramethylsilane was used as internal standard (δ=0) and the values are reported as follows: Chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad), and the coupling constants in Hz. For ^{13}C NMR, $CDCl_3$ (δ=77.27) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution mass spectrometry (MS) and high-resolution MS (HRMS) data were obtained using a VG AutoSpec triple sector MS (electrospray ionization [ESI] ionization). Melting points were measured on measured on a Triad Scientific micromelting point apparatus. Commercially available aryl halides, $Pd(PPh_3)_4$, CuI, and KOH were used without further purification. DME was distilled from CaH under N_2 atmosphere.

General procedure

A mixture of 4-substituted oxazole (1 mmol), aryl bromide (1 mmol), KOH (1 mmol), and CuI (1 mmol) in dimethoxyethane (10 mL) was stirred at RT for 10 min and degassed with argon for 20 min. Then, $Pd(PPh_3)_4$ (5 mol%) was added and reflux for the appropriate time. After completion of the reaction as indicated by thin-layer chromatography, the reaction mixture was quenched with water and extracted with ethyl acetate (2×15 mL). Evaporation of the solvent followed by purification on silica gel afforded the pure disubstituted oxazole.

2,5-Diphenyloxazole (3a)

Solid, m.p.72–74°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14–8.06 (m, 2H), 7.92 (s, 1H), 7.80–7.77 (m, 2H), 7.48–7.36 (m, 5H), 7.31–7.25 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 141.2, 132.7, 130.4, 129.7, 128.0, 127.4, 126.9, 125.9, 125.0 ppm; MS (ESI): *m/z* ($[M+H]^+$): 222; HRMS (ESI): *m/z*calcd for $C_{15}H_{12}NO$: 222.0918; found: 222.0923.

5-phenyl-2-(3,4,5-trimethoxyphenyl)oxazole (3b)

Semi solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–8.09 (m, 2H), 7.86 (s, 1H), 7.47–7.42 (m, 2H), 7.17 (s, 1H), 6.99 (s, 2H), 3.94 (s, 6H), 3.84 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 153.5, 141.8, 133.1, 130.4, 128.7, 127.3, 126.7, 126.4, 106.0, 102.7, 60.9, 56.2, 56.1 ppm; MS (ESI): *m/z* ($[M+H]^+$): 312; HRMS (ESI): *m/z*calcd for $C_{18}H_{17}NO_4Na$: 334.1055; found: 334.1058.

5-phenyl-2-p-tolyloxazole (3c)

Solid, m.p.70–72°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11–8.08 (m, 2H), 7.89 (s, 1H), 7.61–7.54 (m, 2H), 7.47–7.41 (m, 3H), 7.26–7.22 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 2.41 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 150.8, 141.1, 129.7, 128.9, 128.7, 128.0, 126.4, 124.9, 124.3, 123.0, 21.8 ppm; MS (ESI): *m/z* ($[M+H]^+$): 236.

2-(3,4-dimethoxyphenyl)-5-phenyloxazole (3k)

Solid, m.p.98–100°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.10 (m, 2H), 7.53-7.46 (m, 2H), 7.36 (s, 1H), 7.33 (dd, *J* = 1.9 Hz, *J* = 6.3 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 150.7, 148.9, 148.7, 129.7, 128.4, 127.1, 125.7, 121.8, 120.7, 116.9, 111.2, 107.2, 56.1, 56.1 ppm; MS (ESI): *m/z* ($[M+H]^+$): 282.

2-(benzo[d][1,3]dioxol-5-yl)-5-phenyloxazole (3l)

Solid, m.p.136–138°C. ^{1}H NMR (300 MHz, CDCl3) 8.08–8.06 (m, 2H), 7.51–7.48 (m, 3H), 7.33 (s, 1H), 7.26 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 1H), 7.18 (d, *J* = 1.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 2H); MS (ESI): *m/z* ($[M+H]^+$): 266.

5-phenyl-2-p-tolyloxazole (3f)

Solid, m.p.70–72°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13–8.09 (m, 2H), 7.83 (s, 1H), 7.62–7.51 (m, 2H), 7.43–7.40 (m, 3H), 7.2–7.20 (m, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 2.45 (s, 3H) ppm; MS (ESI): *m/z* ($[M+H]^+$): 236.

2-Ethyl-5-phenyloxazole (3g)

Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03–7.96 (m, 2H), 7.44–7.35 (m, 4H), 2.65–2.54 (q, *J* = 8.6 Hz, *J* = 15.0 Hz, 2H), 1.28 (t, *J* = 7.5 Hz,

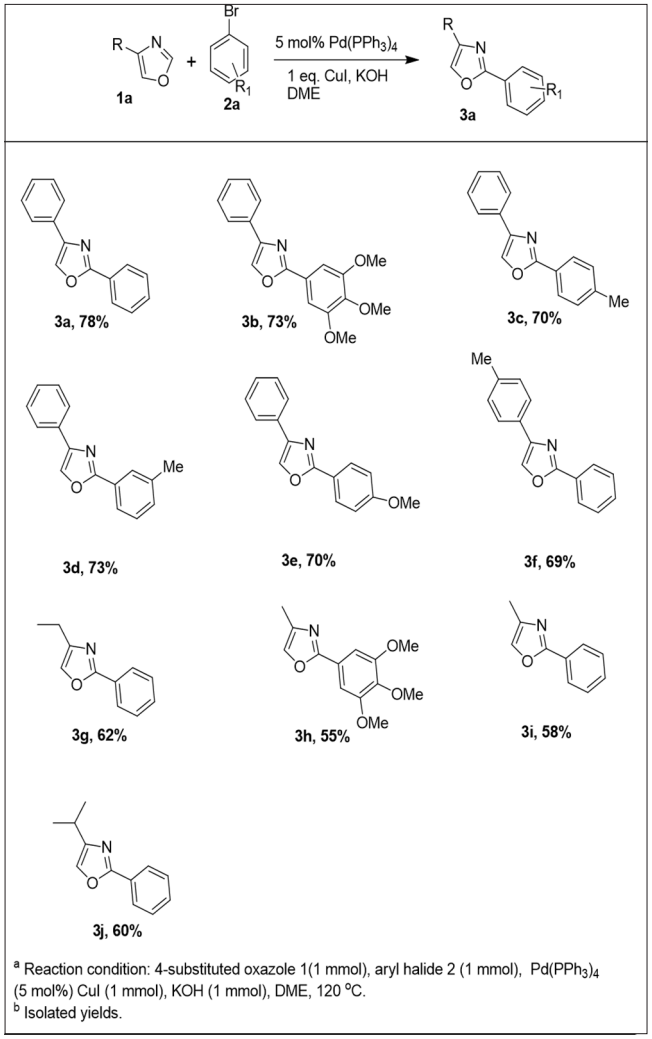

Fig. 3: Reaction screening with different aryl bromides

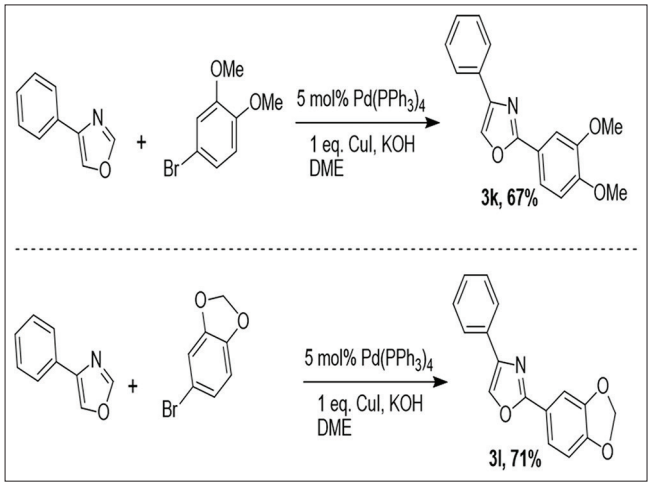

Fig. 4: Synthesis of texamine and balsoxin analogs 3k and 3l

3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 129.7, 128.6, 127.8, 125.9, 122.0, 28.3, 17.2.ppm; MS (ESI): *m/z* ([M+H]$^+$): 174.

5-Phenyl-2-(3,4,5-trimethoxyphenyl)oxazole (3h)

Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 6.87 (s, 2H), 3.90 (s, 6H), 3.82 (s, 3H), 2.50 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 152.5, 139.7, 137.1, 132.1, 126.1, 102.2, 61.0, 56.3, 14.6 ppm;MS (ESI): *m/z* ([M+Na]$^+$): 272; HRMS (ESI): *m/z*calcd for $C_{13}H_{15}NO_4Na$: 272.0898; found: 272.0895.

5-Methyl-2-phenyloxazole (3i)

Semi solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.25–7.21 (m, 1H), 2.50 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 139.8, 132.4, 128.0, 127.2, 124.7, 14.7 ppm; MS (ESI): *m/z* ([M+H]$^+$): 160; HRMS (ESI): *m/z*calcd for $C_{10}H_{10}NO$: 160.0762; found: 160.0769.

2-Isopropyl-5-phenyloxazole (3j)

Semi solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.97 (m, 2H), 7.42-7.37 (m, 3H), 7.33 (d, *J* = 1.0 Hz, 1H), 2.86-2.83 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 158.1, 129.7, 128.6, 127.8, 125.9, 121.7, 26.2, 20.6 ppm; MS (ESI): *m/z* ([M+H]$^+$): 188.

On the basis of these results, a mechanism is proposed; initially, the Pd catalyst reacted with bromo compound 2a in the presence of base and forms species Pd(II) A. Then, A is proposed to interact with oxazole 1a, leading to C–H activation and formation of a palladium(II) aryl-heteroaryl intermediate B, C–C reductive elimination, of which furnishes product 3a. The catalytic cycle is completed when the Pd(0) species is oxidized to Pd(II) by CuI.

CONCLUSION

$Pd(PPh3)_4$ and CuI cocatalytic system direct arylation of 4-aryl/alkyl oxazoles with various aryl bromides has been developed to generate 2,4-disubstituted oxazoles. This methodology is illustrated by an expedient two-step synthesis of the four 2,4-disubstituted oxazoles from commercially available starting materials. 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-disubstituted oxazoles. Studies on additional applications of this direct arylation procedure with aryl/alkyl boronic acids and other heterocycles are in progress in our laboratory.

AUTHORS' CONTRIBUTIONS

Manuscript was prepared by Venkata Reddy Regalla.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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