First Example of Quinoxaline-Directed C–H Activation: A Novel Method for Acetoxylation of Arenes

B. V. Subba Reddy,* K. Ramesh, J. S. Yadav

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India
E-mail: basireddy@iict.res.in

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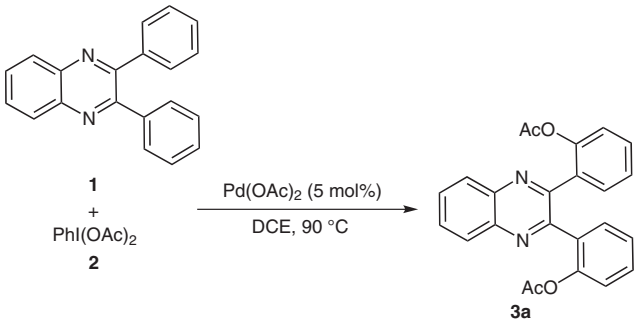
Abstract: 2-Aryl- and 2,3-diarylquinoxalines undergo smooth acetoxylation in the presence of 5 mol% $Pd(OAc)_2$ and a stoichiometric amount of $PhI(OAc)_2$ via C–H activation to produce the corresponding acetoxy-susbstituted quinoxaline derivatives in excellent yields with high regioselectivity.

Key words: hypervalent iodine reagent, aryl quinoxalines, acetoxylation, C–H activation

Quinoxalines have received considerable interest from the pharmaceutical industry because of their interesting properties such as antiviral, antibacterial, anti-inflammatory, and antiprotozoal activities, and as kinase inhibitors.[1] They have also been evaluated as anticancer, anthelmintic, antifungal, and insecticidal agents.[2] Furthermore, the quinoxaline nucleus is a part of several antibiotics such as echinomycin, levomycin, and actinomycin which are known to inhibit the growth of gram-positive bacteria and to be active against various transplantable tumors.[3] Besides this, they have found applications as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents.[4,5]

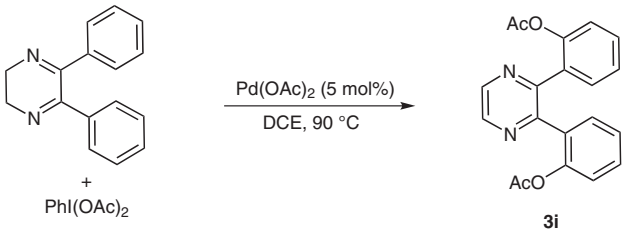
C–H activation is a versatile approach for the direct functionalization of aromatic C–H bonds using transition-metal catalysis.[6,7] Directing groups play a key role in the selective functionalization of C–H bonds,[8] usually possessing a lone pair that can coordinate to the transition-metal catalyst to direct *ortho* functionalization via a five- or six-membered metallacycle.[9]

In continuation of our interest on C–H activation,[10] we herein report a novel method for the acetoxylation of aromatic systems using the $Pd(OAc)/PhI(OAc)_2$ system. In this reaction, $Pd(OAc)_2$ acts as a catalyst to activate the aromatic C–H bond via quinoxaline-directed oxidative insertion. $PhI(OAc)_2$ works as an acetoxylation agent as well as to reoxidize Pd(0) to Pd(II). Initially, we attempted acetoxylation 2,3-diphenylquinoxaline using 2.2 equivalents $PhI(OAc)_2$ in the presence of 5 mol% $Pd(OAc)_2$, and reaction proceeded smoothly at 90 °C in 1,2-dichloroethane affording the bisacetoxylated product **3a** in 84% yield (Scheme 1).



Scheme 1 Bisacetoxylation of 2,3-diphenylquinoxaline

Similarly, various diarylquinoxalines such as 6-methyl, 6,7-dimethyl, 6-nitro, 6-carboxymethyl, 6-bromo, and 6-fluoro derivatives participated well in this reaction. No acetoxylation was observed at the sp^3 C–H in case of methyl-substituted quinoxalines (entries 2, 3, 11, and 12, Table 1), no ester hydrolysis was observed (entries 5 and 14, Table 1) and no dehalogenation occurred (entries 6, 7, and 15, Table 1). Encouraged by the results obtained with arylquinoxalines, we turned our attention to 2,3-diphenylhexahydroquinoxaline and 5,6-diphenyl-2,3-dihydropyrazine. Both substrates underwent smooth acetoxylation along with aromatization under similar conditions to before (entries 8 and 9, Table 1, Scheme 2).



Scheme 2 Bisacetoxylation of dihydropyrazine

These results provided the incentive to study reactions with monoarylated quinoxalines. Thus, treatment of 2-phenylquinoxaline with $PhI(OAc)_2$ in the presence of 5 mol% $Pd(OAc)_2$ gave the monoacetoxylated product in 90% (Scheme 3, Table 1).

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Table 1 $Pd(OAc)_2$-Catalyzed Acetoxylation of Arenes Using $PhI(OAc)_2$

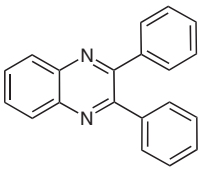
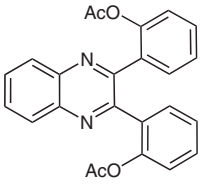
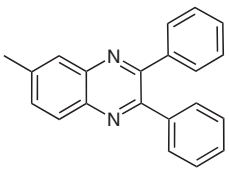
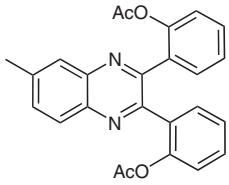
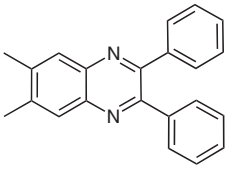
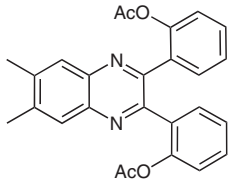
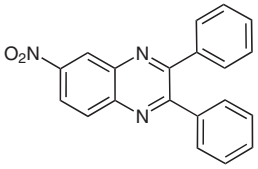
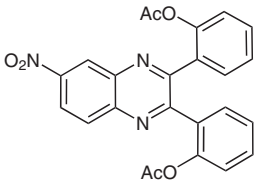
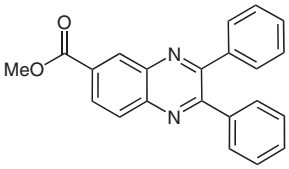
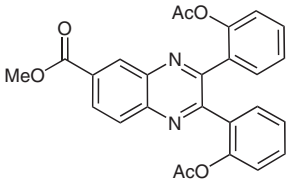
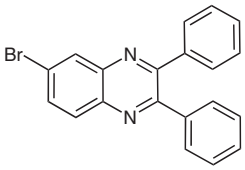
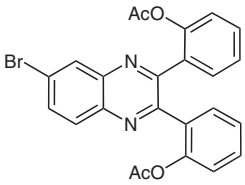
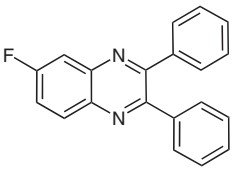
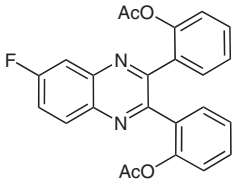
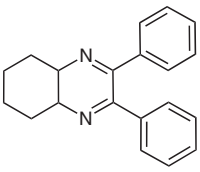
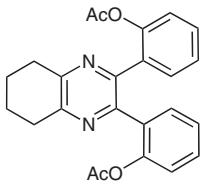
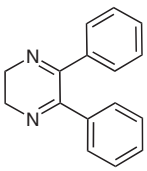
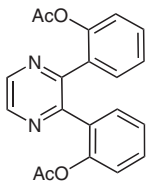
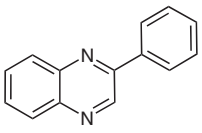
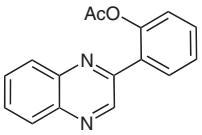
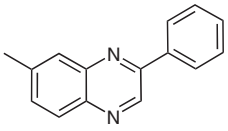
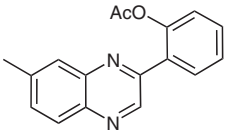
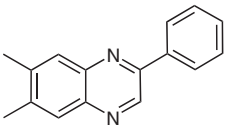
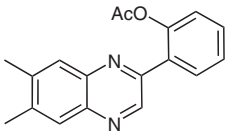
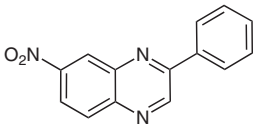
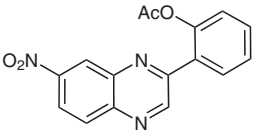
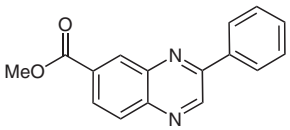
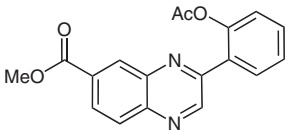
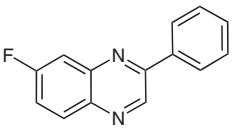
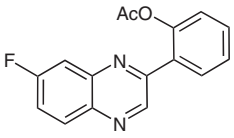
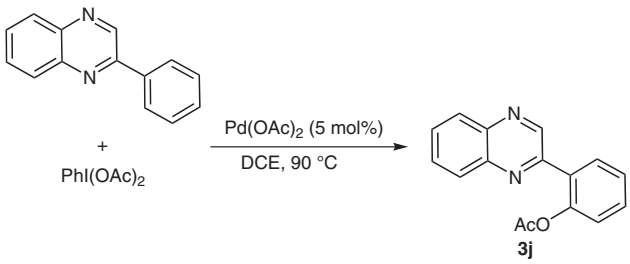
Entry	Arylquinoxaline **1**	Product **2**[a]	Time (h)	Yield (%)[b]
1			12	84[c]
2			11	87[c]
3			10	93[c]
4			15	78[c]
5			15	94[c]
6			14	88[c]
7			15	86[c]
8			11	89[c]
9			10	87[c]

Table 1 $Pd(OAc)_2$-Catalyzed Acetoxylation of Arenes Using $PhI(OAc)_2$ (continued)

Entry	Arylquinoxaline **1**	Product **2**[a]	Time (h)	Yield (%)[b]
10			10	91[d]
11			10	92[d]
12			10	95[d]
13			13	88[d]
14			13	91[d]
15			12	90[d]

[a] The products were characterized by IR, NMR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] Conditions: 2.2 equiv of $PhI(OAc)_2$ were used.
[d] Conditions: 1.1 equiv of $PhI(OAc)_2$ were used



Scheme 3 Monoacetoxylation of 2-phenylquinoxaline

Similarly, various 2-phenylquinoxaline derivatives participated well in this reaction. No acetoxylation was observed in the absence of either $Pd(OAc)_2$ or $PhI(OAc)_2$. Among various oxidants such as AgOAc, $Mn(OAc)_3$, and $Cu(OAc)_2$, $PhI(OAc)_2$ was found to be most effective in terms of conversion. In all cases, the reactions were clean and the products were obtained in excellent yields and characterized by MS, NMR, and IR spectroscopy. The scope and generality of this process is illustrated in Table 1.[11]

Probably, the reaction proceeds by oxidative insertion of Pd(II) into C–H bond via a five-membered transition state as depicted in Scheme 4. Finally, Pd(0) is converted into Pd(II) by $PhI(OAc)_2$ to complete the catalytic cycle.

In summary, we have developed a novel protocol for the acetoxylation of aromatic compounds via C–H activation. The experimental procedure is simple, convenient, and the reaction conditions are amenable to scale-up. This method provides an easy access to acetoxy-substituted quinoxalines with diverse chemical structures for biological evaluation.

Acknowledgment

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References and Notes

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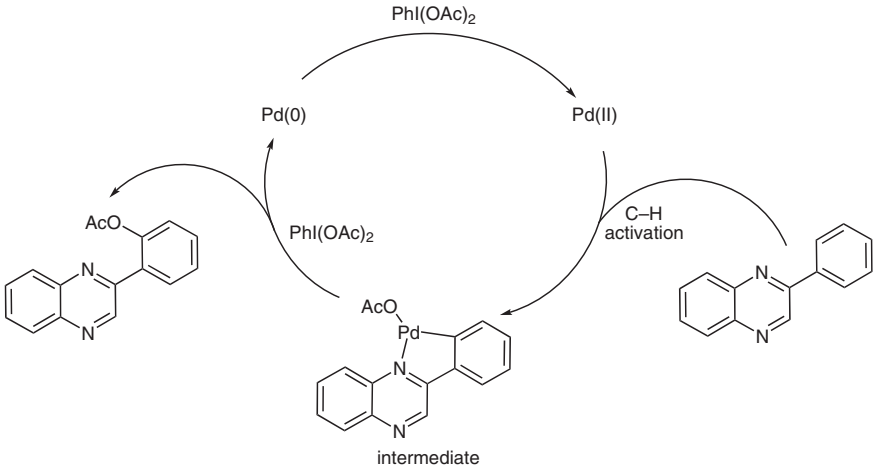

Scheme 4 A plausible reaction pathway

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(11) **Typical Experimental Procedure**

A mixture of 2,3-diphenylquinoxaline (100 mg, 0.35 mmol), $PhI(OAc)_2$ (250 mg, 0.78 mmol), and $Pd(OAc)_2$ (4 mg, 0.05 mmol) in DCE (5 mL) was stirred at r.t. for 10 min, then the resulting mixture was heated to 90 °C for 12 h. After completion of reaction as indicated by TLC, the reaction mixture was filtered, diluted with H_2O and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhyd Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (Merck, 60–120 mesh, EtOAc–hexane, 0.5:9.5) to afford pure bisacetoxy derivative.

Compound **3c**: yellow solid, mp 143–144 °C. IR (KBr): ν_{max} = 3027, 2923, 2854, 1765, 1620, 1458, 1370, 1190, 1116, 1031, 909, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 2.48 (s, 3 H), 7.01–7.07 (m, 2 H), 7.24–7.30 (m, 2 H), 7.79 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 20.8, 123.0, 125.5, 128.8, 129.8, 131.3, 131.4, 139.8, 140.0, 148.2, 149.7, 168.9. MS (EI): *m/z* = 449 [M + Na]. HRMS: *m/z* calcd for $C_{26}H_{22}N_2O_4Na$: 449.1477; found: 449.1475.

Compound **3e**: yellow solid, mp 161–162 °C. IR (KBr): ν_{max} = 3029, 2922, 2852, 1769, 1715,1442, 1374, 1310, 1278, 1254, 1181, 1112, 1054, 1027, 907, 807 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.10 (s, 3 H), 4.03 (s, 3 H), 7.17 (m, 4 H), 7.41 (m, 4 H), 8.18 (s, 1 H), 8.39 (dd, 1 H, *J* = 1.8, 8.6 Hz), 8.85 (d, 1 H, *J* = 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 20.9, 52.6, 123.2, 125.6, 129.4, 129.8, 130.3, 130.6, 130.7, 131.4, 131.6, 131.7, 140.1, 142.7, 148.3, 151.9, 152.7, 166.1, 168.7, 168.8. MS (EI): *m/z* = 479 [M + Na]. HRMS: *m/z* calcd for $C_{26}H_{20}N_2O_6Na$: 479.1219; found: 479.1202.

Compound **3j**: pale yellow solid, mp 103–104 °C. IR (neat): ν_{max} = 3020, 2923, 2852, 1764, 1646, 1544, 1488, 1448, 1369, 1312, 1187, 1108, 1034, 1010, 958, 912, 867, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 7.21 (s, 1 H), 7.39–7.57 (m, 2 H), 7.74–7.80 (m, 2 H), 7.91 (dd, 2 H, *J* = 1.3, 6.2 Hz), 8.21 (m, 2 H), 9.10 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 123.5, 128.1, 129.1, 129.4 129.5, 129.9, 130.2, 130.3, 130.9, 131.1, 141.1, 148.5, 150.8, 169.3. MS (EI): *m/z* = 287 [M + Na]. HRMS: *m/z* calcd for $C_{16}H_{12}N_2O_2Na$: 287.0796; found: 287.0784.