Aromatic Carbonylation Regio-Controlled by Oxazole and Isoxazole Rings. Novel Route to Heterocycle-Substituted *o*-Benzoates

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3,5-Diphenylisoxazole and 2,5-diphenyloxazole were regioselectively carbonylated under an atmosphere of carbon monoxide after the formation of arylpalladium(II) intermediates, to give bioactive *o*-benzoates substituted by isoxazole and oxazole rings in good yields.

Keywords 3,5-diphenylisoxazole; 2,5-diphenyloxazole; carbon monoxide; palladium(II) acetate; regioselective palladation; arylpalladium(II) complex; heterocycle-substituted *o*-benzoate; carbonylation

Many bioactive benzoic acids, esters, or amides (**1**) with heterocyclic rings as *ortho* substituents are known.¹⁾ Most of these compounds have been synthesized by inter- or intramolecular cyclization of acyclic materials containing *o*-carboxyphenyl group,²⁾ as can be seen in the cases of isoxazolylbenzoic acid (**2**) and oxazolylbenzoic acid (**3**), which have hypolipemic, herbicidal, or plant growth-regulatory activity.^{1,3)} The chemistry of insertion of carbon monoxide into metal–carbon bonds⁴⁾ and *ortho*-metallation onto aromatic rings retaining substituents with β -hetero atoms⁵⁾ is well established. However, little attention has been paid to the role of transition metals in the chemistry of oxazoles and isoxazoles.⁶⁾ In an extension of our work on the synthesis of bioactive heterocyclic compounds by novel application of a palladium catalyst,⁷⁾ an attempt was made to synthesize *ortho*-benzoic acids substituted with heterocycles *via* regioselective metallation and subsequent carbonylation of diphenylisoxazole (**4**) and diphenyloxazole (**6**). Herein, we wish to describe palladium(II)-promoted *ortho*-esterification of **4** and **6** using carbon monoxide, and the formation of eight-membered azalactones from **6**, together with related reactions.

A mixture of 3,5-diphenylisoxazole (**4**, 2.5 mmol) and Pd(OAc)₂ (2.5 mmol) in a mixed solvent of acetic acid (60 ml) and carbon tetrachloride (20 ml) was heated at 80 °C for 24 h under an atmosphere of nitrogen. After evaporation of the solvents followed by recrystallization of the residue from benzene–hexane, a yellow-colored Pd-complex (**5**) was isolated in almost quantitative yield. The complex (**5**) was dissolved in a mixed solvent of tetrahydrofuran (THF) and methanol (1 : 1) and the solution was stirred at 0 °C for 20 h under an atmosphere of carbon monoxide. After usual work-up, the ester (**8a**, R = CH₃) was obtained in a yield of 75.9%. A similar palladation of 2,5-diphenyloxazole (**6**) gave the corresponding aryl–palladium(II) complex (**7**) in an isolated yield of 94.5%. Carbonylation of **7** in THF–MeOH at 0 °C for 18 h produced **9a** (R = CH₃, isolated yield of 77.2%). The physical and spectral data of the isolated esters **8a** and **9a** were identical with the literature values for **8a**³⁾ and **9a**.^{8a)} The palladium com-

plexes **5** and **7** showed aromatic absorptions at 725 and 723 cm^{−1}, respectively, attributed to four neighboring hydrogens on an aromatic ring. Furthermore, molecular weight measurements indicated the formation of 1 : 1 complexes between palladium(II) and the heterocycles **4** and **6**. Therefore, **5** and **7** must be aryl–palladium(II) σ -complexes stabilized intramolecularly by the nitrogen in the isoxazole or oxazole ring.

Regioselective palladation of **4** and **6** may reflect the strong coordination ability of nitrogen of the oxazole or isoxazole ring to the palladium atom.⁹⁾ The carbonylation of the aryl–palladium complexes, **5** and **7**, proceeded smoothly under mild conditions in a mixed solvent of THF and methanol, as expected from the literature concerning aromatic carbonylation.¹⁰⁾ However, the use of THF and ethanol as solvents in the carbonylation of **7** resulted in the preferential formation of the oxazole ring-cleaved carbonylation product **10b** and the hydrogenated product **6**. The results of carbonylation of **7** in various solvents are summarized in Table I. The infrared (IR) spectra of **9** showed

two pairs of absorptions diagnostic for a 2,5-diaryloxazole ring¹¹⁾ in each region of 820–850 cm⁻¹ and 760–780 cm⁻¹. The IR spectra of **10** gave only one signal (near 835 cm⁻¹) in the former region and a pair of absorptions in the latter region, indicating cleavage of the oxazole ring. In high-resolution mass analyses, **9** and **10** gave common fragment peaks at m/z 248.0 (C₁₆H₁₀NO₂; M⁺ – alkoxy group) and at m/z 130.0 (C₈H₄NO⁺; *o*-cyanobenzoyl cation). In the ultraviolet (UV) spectra, **9** gave a broad and strong absorption maximum at longer wavelength than 300 nm, owing to the presence of a chain of three aromatic rings, whereas the oxazole ring-cleaved product **10** showed an absorption maximum at near 290 nm. All these spectral data and the following mechanistic consideration on carbonylation of the aryl–palladium intermediate confirmed the identity of the oxazole ring-cleaved products as the azaheptanolides **10**. The carbon-13 nuclear magnetic resonance (¹³C-NMR) signals of **9a** and **10a** were assigned as shown in Fig. 1, in comparison with those of oxazoles appearing in the literature.¹²⁾

It can be seen in Table I that steric hindrance by alkyl groups of the alcohols would lead to cleavage of the oxazole rings during alcoholysis of the carbonylated intermediate **11** to give the ring-enlarged carbonylation products **10**. The

TABLE I. Carbonylation of Pd(II)-Aryl σ -Complex **7** in Various Alcohols^{a)}

Alcohol ^{b)} R-OH	Solvent ^{b)}	Conv. of 7 (%)	Products (%) ^{c)}		
			9	10	6
R=CH ₃	THF	95.7	77.2	8.9	2.1
CH ₃	None	93.7	74.7	Trace	Trace
C ₂ H ₅	THF	94.4	10.1	20.2	33.3
C ₂ H ₅	None	84.3	22.8	13.1	25.6
CH(CH ₃) ₂	THF	84.9	20.4	14.2	29.7
CH(CH ₃) ₂	None	43.6	27.8	8.0	54.6
C(CH ₃) ₃	THF	30.9	None	None	98.4

a) Carbonylation was carried out at 0 °C for 18 h under an atmosphere of CO. b) Mixed alcohol (50 ml) and THF (50 ml) or neat alcohol (100 ml) was used as the reaction medium. c) Yields are based on consumed **7**.

mechanism may involve a nucleophilic attack of alcohol at the 2-position of the oxazole ring in the benzoyl–palladium intermediate (**12**) to cause enlargement of the oxazole ring followed by reductive elimination of palladium (Chart 1). Furthermore, the presence of *tert*-butanol, which has the bulkiest alkyl group among the alcohols used, increased the formation of the hydrogenated product **6**, reflecting the difficulty of nucleophilic attack of *tert*-butanol on **11**. The results may be characteristic of *ortho*-heterocycle substituted aryl or benzoyl palladium complexes, since similar effects of bulkiness of the alkyl groups in alcohols are unknown in alcoholysis of unsubstituted phenyl or benzoyl palladium species.¹³⁾ The products **9** and **10** were hydrated under acidic or basic conditions to obtain the corresponding acids. Interestingly, both products gave comparable results. Namely, the oxazolybenzoate **9a** gave the *o*-oxazolybenzoic acid (**3**) in an isolated yield of 86% only under acidic conditions (concentrated HCl/ethanol), although an intractable mixture was formed under basic conditions (aqueous NaOH/ethanol), owing to decomposition of the oxazole ring. On the other hand, **10b** gave rise to a corresponding imidoalcohol (**10d**) only under basic conditions, in contrast to the formation of a mixture of complex and unidentified products under acidic conditions. Compound **10d** showed an ester absorption at 1712 cm⁻¹ and three absorptions similar to those of **10** in a region of 750–792 cm⁻¹ in the IR spectrum, and fragment peaks at m/z 248 (C₁₆H₁₀NO₂; M⁺ – OH) and at m/z 132 (C₈H₄O₂⁺; phtharoyl cation) in the MS. These spectral data indicated that **10d** still retains the eight-membered lactone ring. The difficult hydrolysis of the lactone under basic conditions might be owing to probable sterical compression of the eight-membered ring with the two benzene rings, preventing nucleophilic attack of hydroxide ions on the ester carbon in **10b**.

A one-pot synthesis of **9a** from **6** was attempted. A mixture of **6** and palladium(II) acetate (molar ratio 1:1) was stirred in a mixed solvent of acetic acid and methanol at 80 °C for 2 h under a nitrogen atmosphere, followed by further stirring of the reaction mixture after addition of an appropriate amount of tetrahydrofuran at the same temperature for 18 h under a normal pressure of carbon monoxide. After usual treatment of the reaction mixture, **9a** was isolated in a yield of 43%, along with a trace of **10a**. Isoxazole and oxazole rings are known to be unstable to oxidative or reductive agents.¹⁴⁾ In the present reactions, however, formation of stable *o*-metallated complexes and subsequent carbonylation under very mild conditions (1 atm CO) were successfully accomplished in THF–MeOH or in MeOH. Therefore, the palladation and subsequent carbonylation of aryl-substituted nitrogen-heterocycles are useful as a facile synthetic method for bioactive benzoic acid derivatives (**1**), since many known reoxidants of zerovalent palladium would be able to change the stoichiometric reactions to Pd-catalyzed reactions.¹⁵⁾

Experimental

All melting points were measured by using a Yanagimoto MP apparatus and are uncorrected. UV spectra were recorded on a Hitachi 228 double beam spectrometer. IR spectra were recorded on a JASCO IRA-100 spectrometer. ¹H- and ¹³C-NMR spectra were taken on JEOL PMX-60 and JNM-EX-90 instruments, respectively. Chemical shifts are given as values from tetramethylsilane as an internal standard. MS were recorded

with a JEOL JMS-01SG mass spectrometer. Molecular weights were measured with a Corona VPO-114 apparatus. THF was used after distillation from sodium. All alcohols were dried on anhydrous sodium sulfate before use. 3,5-Diphenylisoxazole (**4**) was synthesized from benzalacetophenone according to the reported method.¹⁶ 2,5-Diphenyl-oxazole (**6**) and palladium(II) diacetate were commercial products, and used after recrystallization.

***o*-(5-Phenyl-3-isoxazolyl)phenylpalladium(II) Acetate (**5**)** 3,5-Diphenylisoxazole **4** (553 mg, 2.5 mmol) and palladium(II) diacetate (560 mg, 2.5 mmol) were dissolved in a mixed solvent of acetic acid (60 ml) and carbon tetrachloride (20 ml), and stirred at 80 °C for 24 h under nitrogen. After filtration of the reaction mixture and removal of solvents from the filtrate by evaporation, the residue was recrystallized twice from benzene-hexane to give a yellow solid, **5** (940 mg, 99%) mp > 180 °C (dec.). IR (KBr disk) ν : 1580, 1415 (–OAc), 1505, 1463, 1342, 1017, 943, 760, 725 (–C₆H₅). ¹H-NMR (CDCl₃) δ : 2.28 (3H, s, –OAc), 6.13 (1H, s, 4C-H), 6.26–6.97 (4H, m, 3C-Ph-H), 7.42 (5H, s, 5C-Ph-H). MW (VPO method, benzene): Calcd for C₁₇H₁₃NO₃Pd: 385.7. Found: 401.6. Anal. Calcd for C₁₇H₁₃NO₃Pd: Pd, 27.6. Found: Pd, 27.4.

***o*-(5-Phenyl-2-oxazolyl)phenylpalladium(II) Acetate (**7**)** A similar reaction of 2,5-diphenyloxazole **6** (2.21 g, 10 mmol) and palladium(II) diacetate (2.25 g, 10 mmol) in a mixed solvent of acetic acid (60 ml) and carbon tetrachloride (40 ml) gave **7** (3.62 g, 94.0%) as a yellow solid, mp > 175 °C (dec.). IR (KBr disk) ν : 1565, 1412 (–OAc), 1460, 1152, 935, 840, 810, 770, 761, 723 (–C₆H₄), 720, 682 cm^{–1} (–C₆H₅). ¹H-NMR (CDCl₃) δ : 2.20 (3H, s, –OAc), 6.48 (1H, s, 4C-H), 6.23–6.85 (4H, m, 2C-Ph-H), 7.28 (5H, s, 5C-Ph-H). MW (VPO method, benzene): Calcd for C₁₇H₁₃NO₃Pd: 385.7. Found: 383.3. Anal. Calcd for C₁₇H₁₃NO₃Pd: Pd, 27.6. Found: Pd, 28.1.

Methyl *o*-(5-Phenyl-3-isoxazolyl)benzoate (8a**)** The palladium complex (**5**, 184 mg, 0.477 mmol) was dissolved in a mixed solvent of methanol (50 ml) and tetrahydrofuran (50 ml) and allowed to react with carbon monoxide (at atmospheric pressure) at 0 °C for 20 h. Metallic palladium was precipitated during the reaction. After a filtration of the reaction mixture and evaporation of the filtrate, the residual mixture was separated by silica gel column chromatography. Elution with benzene and ethyl acetate gave a pale yellow liquid (133.3 mg), along with the reduced product (**4**, 13.7 mg, 0.06 mmol). The yellow oil was purified by preparative TLC to give the ester **8a** (101 mg, 75.9%). IR (KBr disk) ν : 1725, 1285, 1263 (–COOCH₃), 1440, 1430, 1400, 1080, 945, 768, 723 (–C₆H₄–), 720, 685 cm^{–1} (–C₆H₅). ¹H-NMR (CDCl₃) δ : 3.78 (3H, s, –CH₃), 6.60 (1H, s, 4-H), 7.33–8.20 (9H, m, arom-H). MS m/z (relative int.): 279 (M⁺, 30), 248 (8.5), 220 (3.8), 105 (100), 77 (47.6). These spectral data were identical with those reported for **8a**.³¹

Methyl *o*-(5-Phenyl-2-oxazolyl)benzoate (9a**)** The palladium complex (**7**, 300 mg, 0.778 mmol) was dissolved in a mixed solvent of methanol (50 ml) and THF (50 ml), and allowed to react with carbon monoxide (at atmospheric pressure) at 0 °C for 18 h. Metallic palladium precipitated during the reaction. After treatment as in the case of **8a**, the ester **9a** was isolated as a colorless solid (167 mg, 0.60 mmol), mp 80–81 °C (hexane) [lit. 77–79 °C].^{8a} UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 303 (1.56 × 10⁴), 204 (1.62 × 10⁴). IR (KBr disk) ν : 1717, 1282, 1258 (–COOCH₃), 1480, 1440, 1120, 1103, 1054, 950, 860, 823, 772, 760, 738 (–C₆H₄), 706, 685 cm^{–1} (–C₆H₅). ¹H-NMR (CDCl₃) δ : 3.88 (3H, s, –OCH₃), 7.23–8.17 (10H, m, 4-H and aromatic H). ¹³C-NMR data are shown in Fig. 1. MS m/z (relative int.): 279 (M⁺, 42.7), 248 (8.5), 236 (9.6), 165 (3.8), 130 (8.5), 105 (100), 77 (11.1). 10MMS: Calcd for C₁₇H₁₃NO₃: 279.0894. Found: 279.0804.

Carbonylation of **7 in Various Solvents** Similar reactions of **7** with carbon monoxide in the presence of various alkanols, followed by analogous treatment, were carried out to give the corresponding *o*-(5-phenyl-2-oxazolyl)benzoates (**9**), 6-alkoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (**10**), and the demetallated product (**6**). The products were characterized as follows;

Ethyl *o*-(5-Phenyl-2-oxazolyl)benzoate (9b**)** Colorless oil. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 302 (1.50 × 10⁴), 203 (2.31 × 10⁴). IR (KBr disk) ν : 1720, 1280, 1250,

(–COOEt), 1585, 1542, 1480, 1445, 1360, 1183, 1133, 1100, 1056, 1020, 951, 850, 822, 766, 760, 730, 710, 683 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.18 (t, 3H, –Me), 4.90 (q, 2H, –CH₂–), 7.23–8.32 (m, 10H, 4-H and aromatic H). MS m/z (relative intensity): 293 (M⁺, 83.8), 248 (17.2), 236 (58.6), 130 (28.7), 105 (100), 77 (49.7). 10MMS: Calcd for C₁₈H₁₅NO₃: 293.1052. Found: 293.1099.

Isopropyl *o*-(5-Phenyl-2-oxazolyl)benzoate (9c**)** Colorless oil. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 301 (1.57 × 10⁴), 197 (3.25 × 10⁴). IR (KBr disk) ν : 1720, 1280 (–COO–iso-Pr), 1480, 1462, 1447, 1368, 1343, 1175, 1100, 1056, 950, 915, 850, 820, 768, 760, 732, 710, 683 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.20 (d, 6H, –Me), 5.22 (sp, 1H, –CHMe₂), 7.20–8.15 (m, 10H, 4-H and aromatic H). MS m/z (relative intensity): 307 (M⁺, 80.1), 265 (62.4), 248 (14.7), 221 (20.5), 105 (> 100), 77 (100). 10MMS: Calcd for C₁₉H₁₇NO₃: 307.1208. Found: 307.1142.

6-Methoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (10a**)** mp 88–89 °C. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 292 (1.55 × 10⁴), 196 (2.08 × 10⁴). IR (KBr disk) ν : 1720, 1638, 1610, 1565, 1493, 1455, 1325, 1280, 1225, 1215, 1100, 1072, 1010, 815, 790, 773, 760, 705, 680 cm^{–1}. ¹H-NMR (CDCl₃) δ : 3.93 (s, 3H, –OCH₃), 7.30–7.70 (m, 6H, 4-H and aromatic H), 7.95–8.33 (m, 4H, aromatic H). ¹³C-NMR data are shown in Fig. 1. MS m/z (relative intensity): 279 (M⁺, 100), 248 (18.0), 130 (14.5), 105 (80.2), 77 (46.7). 10MMS: Calcd for C₁₇H₁₃NO₃: 279.0894. Found: 279.0879.

6-Ethoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (10b**)** Colorless oil. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 293 (1.82 × 10⁴), 204 (1.93 × 10⁴). IR (KBr disk) ν : 1710, 1635, 1605, 1580, 1483, 1438, 1365, 1338, 1313, 1230, 1215, 1100, 1090, 1060, 1023, 1015, 832, 780, 767, 753, 700, 680 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.43 (t, 3H, –CH₃), 4.48 (q, 2H, –CH₂–), 7.38–7.64 (m, 6H, 4-H and aromatic H), 7.93–8.33 (m, 4H, aromatic H). MS m/z (relative intensity): 293 (M⁺, 83.9), 248 (17.2), 236 (58.6), 130 (28.8), 105 (100), 77 (49.7). 10MMS: Calcd for C₁₈H₁₅NO₃: 293.1052. Found: 293.1011.

6-Isopropoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (10c**)** Colorless oil. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 296 (1.55 × 10⁴), 196 (3.23 × 10⁴). IR (KBr disk) ν : 1715, 1635, 1615, 1590, 1565, 1492, 1450, 1372, 1317, 1218, 1195, 1102, 1095, 1070, 1005, 995, 920, 843, 792, 778, 762, 710, 687 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.38 (d, 6H, –CH₃), 5.33 (sp, 1H, –CH–), 7.28–8.33 (m, 10H, 4-H and aromatic H). MS m/z (relative intensity): 307 (M⁺, 81.3), 248 (15.0), 130 (9.2), 105 (100), 77 (70.4). 10MMS: Calcd for C₁₉H₁₇NO₃: 307.1208. Found: 307.1135.

Hydrolysis of **9a and **10b** under Acidic Conditions** Methyl *o*-(5-phenyl-2-oxazolyl)benzoate **9a** (115 mg, 0.41 mmol) was dissolved in a mixed solvent (40 ml) of water and ethanol (1:3) and, after addition of 6*M* hydrochloric acid (5 ml), was refluxed under heating for 1.5 h under an atmosphere of nitrogen. After usual work-up, extraction of an acidified aqueous solution (at pH 2) of the acidic products with ethyl ether gave corresponding benzoic acid **3**, which was recrystallized from water-methanol (93 mg, 0.35 mmol).

***o*-(5-Phenyl-2-oxazolyl)benzoic Acid (**9d**)** mp 196–197 °C [lit. 191.5–193.5 °C].^{8b} IR (KBr) ν : 2920–2320, 1705, 1275, 1258, 1140, 1132, 781, 770, 740, 692 cm^{–1}. ¹H-NMR (*d*₄-methanol) δ : 7.24–8.12 (m, 10H, 4-H and aromatic H), MS m/z : 265 (M⁺), 221, 165, 105, 77. An analogous hydrolysis of **10b** under acidic conditions gave a complex product mixture, the component of which were not identified.

Hydrolysis of **9a and **10b** under Basic Conditions** The ethoxyazalactone **10b** (76 mg, 0.26 mmol) was dissolved in a mixed solvent of water and ethanol (1:3) and, after addition of sodium hydroxide (15 mg), was refluxed under heating for 4 h under an atmosphere of nitrogen. After usual treatment, the ether extraction of the acidic fraction of the products gave a colorless solid (**10d**) in a yield of 74%.

6-Hydroxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (10d**)** mp 97.5–98.5 °C. IR (KBr) ν : 2720–2990, 1710, 1630, 1605, 1580, 1485, 1435, 1380, 1210, 1180, 1110, 780, 770, 760, 705, 680 cm^{–1}. ¹H-NMR (*d*₄-methanol) δ : 7.30–7.65 (m, 6H, =CH and aromatic H), 7.93–8.40 (m, 4H, aromatic H). MS m/z : 265 (M⁺), 248, 221, 165, 143, 132, 105, 77. 10MMS: Calcd for C₁₆H₁₁NO₃: 265.0739. Found: 265.0684. An analogous hydrolysis of **9a** under basic conditions gave a complex product mixture, the components of which were not identified.

One-Pot Synthesis of **9a from **6**** 2,5-Diphenyloxazole (**6**, 1.0 mmol) and palladium(II) acetate (1.0 mmol) were dissolved in a mixed solvent (50 ml) of methanol and acetic acid (1:1) and stirred at 80 °C for 2 h under an atmosphere of nitrogen. The brown solution gradually became yellow. Afterwards, THF (50 ml) was added to the reaction mixture. Further stirring was carried out at 80 °C for 18 h under bubbling of carbon monoxide at normal pressure. During the reaction, metallic palladium was precipitated. After usual work-up, the *o*-carbonylated product **9a** was isolated in a yield of 43%. The yield was based on used **6**.

Fig. 1. ¹³C-NMR Spectral Data for **9a** and **10a** in CDCl₃

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