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

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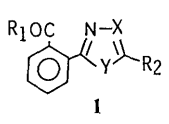
3,5-Diphenylisoxazole and 2,5-diphenyloxazole were regioselectively carbonylated under an atmosphere of carbon monoxide after the formation of arylpalladium(II) intermediates, to give bioactive *o*-benzoates substituted by isoxazole and oxazole rings in good yields.

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 bonds[4] and *ortho*-metallation onto aromatic rings retaining substituents with β-hetero atoms[5] 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.



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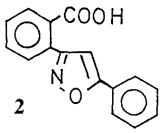

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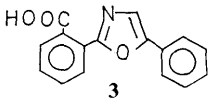

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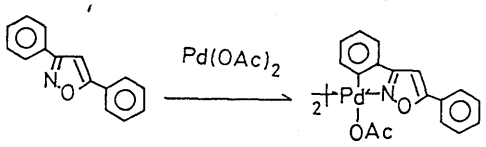
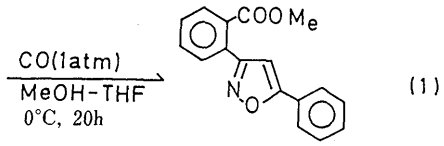
A mixture of 3,5-diphenylisoxazole (**4**, 2.5 mmol) and $Pd(OAc)_2$ (2.5 mmol) in a mixed solvent of acetic acid (60 ml) and carbon tetrachloride (20 ml) was heated at 80 °C for 24 h under an atmosphere of nitrogen. After evaporation of the solvents followed by recrystallization of the residue from 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 = CH_3) 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 = CH_3, 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 complexes **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.

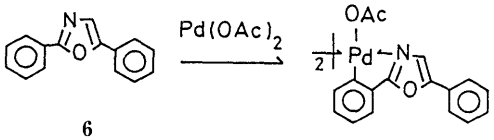


4 **5**

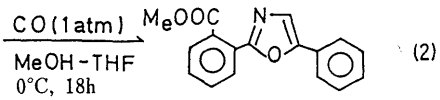


(1)

8a



6 **7**



(2)

9a

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 ring[11] 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 ($C_{16}H_{10}NO_2$; M^+ −alkoxy group) and at *m/z* 130.0 ($C_8H_4NO^+$; *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 (^{13}C-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

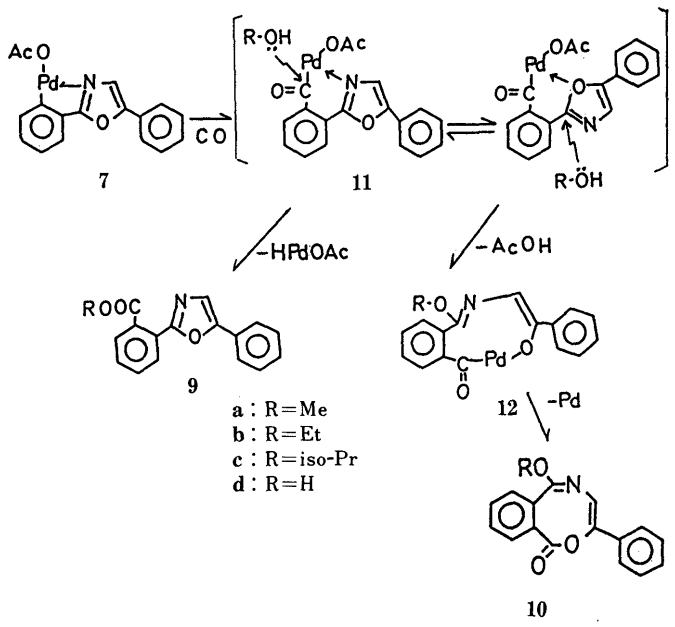


Chart 1

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_2H_5	THF	94.4	10.1	20.2	33.3
C_2H_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 oxazolylbenzoate **9a** gave the *o*-oxazolylbenzoic 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 imidoyl alcohol (**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 ($C_{16}H_{10}NO_2^+$; M^+ −OH) and at *m/z* 132 ($C_8H_4O_2^+$; 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. ^{1}H- and ^{13}C-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-Diphenyloxazole (**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 (*o*-C_6H_4), 718, 690 cm^{-1} (–C_6H_5). ^{1}H-NMR ($CDCl_3$) 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 $C_{17}H_{13}NO_3Pd$: 385.7. Found: 401.6. *Anal.* Calcd for $C_{17}H_{13}NO_3Pd$: 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 (*o*-C_6H_4), 720, 682 cm^{-1} (–C_6H_5). ^{1}H-NMR ($CDCl_3$) 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 $C_{17}H_{13}NO_3Pd$: 385.7. Found: 383.3. *Anal.* Calcd for $C_{17}H_{13}NO_3Pd$: 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 (–$COOCH_3$), 1440, 1430, 1400, 1080, 945, 768, 723 (*o*-C_6H_4-), 720, 685 cm^{-1} (–C_6H_5). ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, –CH_3), 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**.[3]

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 λ_{max}^{MeOH} nm (ε): 303 (1.56×10^4), 204 (1.62×10^4). IR (KBr disk)ν: 1717, 1282, 1258 (–$COOCH_3$), 1480, 1440, 1120, 1103, 1054, 950, 860, 823, 772, 760, 738 (*o*-C_6H_4), 706, 685 cm^{-1} (–C_6H_5). ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s, –OCH_3), 7.23—8.17 (10H, m, 4-H and aromatic H). ^{13}C-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 $C_{17}H_{13}NO_3$: 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 (λ_{max}^{MeOH} nm (ε): 302 (1.50×10^4), 203 (2.31×10^4). 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}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (t, 3H, –Me), 4.90 (q, 2H, –CH_2–), 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 $C_{18}H_{15}NO_3$: 293.1052. Found: 293.1099.

Isopropyl *o*-(5-Phenyl-2-oxazolyl)benzoate (**9c**): Colorless oil. UV λ_{max}^{MeOH} nm (ε): 301 (1.57×10^4), 197 (3.25×10^4). 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}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, 6H, –Me), 5.22 (sp, 1H, –$CHMe_2$), 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 $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1142.

6-Methoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (**10a**): mp 88—89 °C. UV λ_{max}^{MeOH} nm (ε): 292 (1.55×10^4), 196 (2.08×10^4). 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}. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (s, 3H, –OCH_3), 7.30—7.70 (m, 6H, 4-H and aromatic H), 7.95—8.33 (m, 4H, aromatic H). ^{13}C-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 $C_{17}H_{13}NO_3$: 279.0894. Found: 279.0879.

6-Ethoxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (**10b**): Colorless oil. UV λ_{max}^{MeOH} nm (ε): 293 (1.82×10^4), 204 (1.93×10^4). 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}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (t, 3H, –CH_3), 4.48 (q, 2H, –CH_2–), 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 $C_{18}H_{15}NO_3$: 293.1052. Found: 293.1011.

6-Isopropyloxy-3-phenyl-5-aza-2(1*H*)-oxabenzocyclooctatetraen-1-one (**10c**): Colorless oil. UV λ_{max}^{MeOH} nm (ε): 296 (1.55×10^4), 196 (3.23×10^4). IR 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}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (d, 6H, –CH_3), 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 $C_{19}H_{17}NO_3$: 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}. ^{1}H-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}. ^{1}H-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 $C_{16}H_{11}NO_3$: 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**.

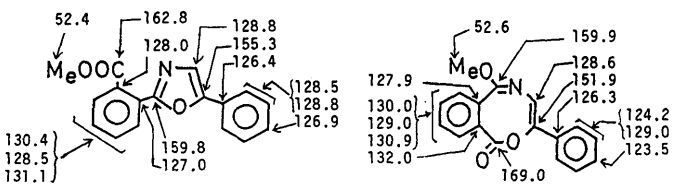


Fig. 1. ^{13}C-NMR Spectral Data for **9a** and **10a** in $CDCl_3$

References and Notes

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