Condensed Heteroaromatic Ring Systems. XX.[1] Palladium-Catalyzed Carbonylative Coupling of Iodobenzenes with (*Z*)-1-Ethoxy-2-(tributylstannyl)ethene

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Palladium-catalyzed cross-coupling reaction of iodobenzene and its 4-substituted derivatives, except for 4-nitroiodobenzene, with (*Z*)-1-ethoxy-2-(tributylstannyl)ethene under a carbon monoxide atmosphere (5 atm) gave the corresponding (*E*)-3-ethoxy-1-arylprop-2-en-1-ones in considerable yields. Syntheses of chromone and 4(1*H*)-quinolinone were accomplished by application of this method to 2-(methoxymethoxy)iodobenzene and ethyl 2-iodophenylcarbanylate, respectively. The results obtained on the carbonylative coupling reaction of halopyridines are also described.

Keywords palladium-catalyzed reaction; (*Z*)-1-ethoxy-2-(tributylstannyl)ethene; carbon monoxide; chromone; 4(1*H*)-quinolinone; iodobenzene; iodopyridine

Previously, we reported the palladium-catalyzed cross-coupling reaction of aryl bromides with (*Z*)-1-ethoxy-2-(tributylstannyl)ethene (**3**), and its application for construction of various condensed heteroaromatic ring systems.[2] In the present paper, we describe the carbonylative coupling reaction of **3** with iodobenzenes under a carbon monoxide atmosphere, carried out as an extension of the previous investigation.

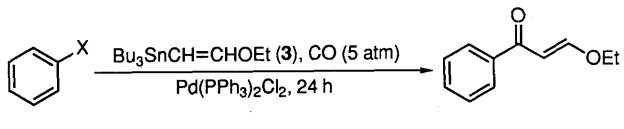
In 1979, Tanaka[3] reported that the carbonylative coupling reaction of iodobenzene with tetramethylstannane under a carbon monoxide atmosphere (30 atm) was highly promoted by the catalytic action of iodo(phenyl)bis(triphenylphosphine)palladium [$PhPdI(PPh_3)_2$] to give methyl phenyl ketone. To our knowledge, this is the first reported example of the palladium-catalyzed carbonylative coupling reaction of aromatic halides with stannane derivatives. Later, Stille *et al.*[4] reported the carbonylative coupling reaction of 4-substituted iodobenzenes with 1-ethoxy-1-(trimethylstannyl)ethene in the presence of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$]. The subsequent ozonolysis of the products, 2-ethoxy-1-(4-substituted phenyl)prop-2-en-1-ones, provides a general method for the synthesis of ethyl α-oxophenylacetates, although the reaction appears to be hindered by a 4-nitro group in the benzene moiety.

In connection with the above reports, the same group[5] found that 4-substituted phenyl triflates smoothly reacted with 1-(trimethylstannyl)-2-phenylethene and carbon monoxide under the catalytic action of dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium [$Pd(dppf)Cl_2$] to give 3-phenyl-1-(4-substituted phenyl)prop-2-en-1-ones in satisfactory yields.

Based on these findings, we investigated the carbonylative coupling reaction of aryl and heteroaryl halides with **3**, and have reached the conclusion that the reaction starting from aryl iodides has utility for the synthesis of (*E*)-3-ethoxy-1-arylprop-2-en-1-ones.

Firstly, in order to estimate general reaction conditions, the reactions of iodobenzene (**1a**) and bromobenzene (**2**) were investigated. As shown in Table I, **1a** appeared to be a much better substrate than **2** judging from the yields of (*E*)-3-ethoxy-1-phenylprop-2-en-1-one (**4a**), and chloroform was concluded to be the most favorable among the solvents tested. The presence of tetraethylammonium chloride in the reaction mixture was not effective for improving the product yields.

Then, five kinds of 4-substituted iodobenzenes (**1b—f**)



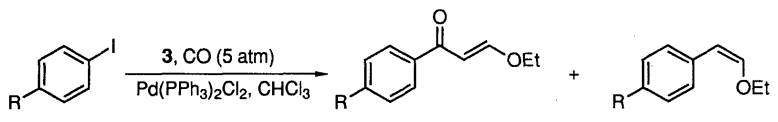
1a : X = I
2 : X = Br

4a

Chart 1

TABLE I. Palladium-Catalyzed Carbonylative Coupling Reaction of Halobenzenes with **3**

Substrate	Solvent	Additive	Reaction temp. (°C)	Yield (%)
1a	DMF	Et_4NCl	80	23
1a	THF	—	80	50
1a	C_6H_6	—	80	40
1a	$CHCl_3$	—	80	60
2	THF	—	100	0
2	$CHCl_3$	—	100	0
2	$CHCl_3$	—	100	0



1b—f **4b—f** **5e,f**

b : R = Me	69%	0%
c : R = OMe	68	0
d : R = NHAc	71	0
e : R = COOEt	59	26
f : R = NO_2	25	40

Chart 2

were employed as substrates for the reaction. Electron-donating groups such as methoxyl, methyl, and acetylamino groups were observed to promote the carbonylative coupling reaction, whereas electron-withdrawing groups, especially the nitro group, were unfavorable. In the case of 4-nitroiodobenzene (**1f**), the carbonylative coupling reaction was rather hindered, and (*Z*)-2-ethoxy-1-(4-nitrophenyl)-ethene (**5f**) was obtained as a major product. This substituent effect is the reverse of the one reported previously in the cross-coupling reaction of 4-substituted bromobenzenes with **3**.[2)]

Retardation of the carbonylative coupling reaction by electron-withdrawing groups as described above was also observed in the reaction of iodopyridines with **3**. That is, the reaction of 3-iodopyridine (**6**), which has a leaving group on a less electron-deficient position of the pyridine nucleus, with **3** under the same conditions gave (*E*)-3-ethoxy-1-(3-pyridinyl)prop-2-en-1-one (**7**) in 44% yield, and the reaction of 2-iodopyridine (**8a**) which is a pyridine derivertive with a leaving group at an electron-deficient position, gave the corresponding (*Z*)-2-(2-ethoxyethen-1-yl)pyridine (**9**) in a low yield. In addition, 2-bromopyridine (**8b**) gave **9** in 8% yield.

Finally, the synthesis of chromone (**12**) and 4(1*H*)-quinolinone (**15**) was achieved by application of this method, as shown in Chart 4. The (*E*)-3-ethoxy-1-(2-substituted phenyl)propenones **11** and **14** obtained by the carbonylative coupling reaction of the corresponding iodobenzenes **10** and **13** smoothly underwent the cyclization under acidic conditions to give the expected products **12** and **15**, respectively.

Miyaura *et al.*[6)] have reported that the palladium-catalyzed reaction of halobenzenes with (*E*)-tris(2-ethoxyethenyl)borane gives (*E*)-1-ethoxy-2-phenylethenes in good yields, but there is no report dealing with the introduction of a (2-ethoxyethenyl)carbonyl group into an aromatic ring by the carbonylative coupling reaction with an organoboron compound. Accordingly, on the basis of the results described in the previous[2)] and present paper, the reaction with **3** seems to have utility for the introduction of 2-ethoxyethenyl- and (2-ethoxyethenyl)carbonyl groups into an aromatic ring and for the construction of condensed heteroaromatic ring systems.

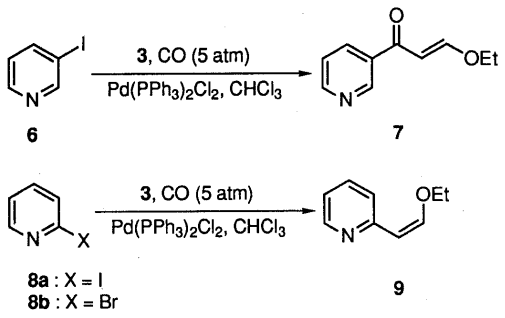


Chart 3

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a JMX-AX500 mass spectrometer. Liquid products were purified by Kugelrohr distillation. Boiling points are oven temperatures.

General Procedure for the Palladium-Catalyzed Carbonylative Coupling Reaction of Aryl Halides with (*Z*)-1-Ethoxy-2-(tributylstannyl)ethene (3) A mixture of an aryl iodide (1 mmol), **3** (1 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), and $CHCl_3$ (6 ml) was heated under a carbon monoxide (5 atm) atmosphere at 80 °C for 5—24 h in a sealed apparatus. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by distillation or recrystallization.

(*E*)-3-Ethoxy-1-phenylprop-2-en-1-one (**4a**): A colorless liquid; bp 110—120 °C/4 mmHg (lit.[7)] bp 156—158 °C/28 mmHg). ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, J=6 Hz), 4.05 (2H, q, J=6 Hz), 6.43 (1H, d, J=12 Hz), 7.78 (1H, d, J=12 Hz), 7.2—7.7 (3H, m), 7.8—8.1 (2H, m). IR ($CHCl_3$) cm^{-1}: 1682. MS *m/z* (relative intensity): 176 (M^+, 36), 161 (13), 147 (34), 131 (22), 105 (60), 99 (54), 77 (66), 71 (100). HRMS Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0847.

(*E*)-3-Ethoxy-1-(4-methylphenyl)prop-2-en-1-one (**4b**): A colorless liquid, bp 110 °C/0.3 mmHg. ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, J=7 Hz), 2.35 (3H, s), 4.00 (2H, q, J=7 Hz), 6.34 (1H, d, J=12 Hz), 7.20 (2H, d, J=8 Hz), 7.70 (1H, d, J=12 Hz), 7.75 (2H, d, J=8 Hz). IR ($CHCl_3$) cm^{-1}: 1660. MS *m/z* (relative intensity): 190 (M^+, 32), 175 (13), 161 (21), 147 (37), 131 (35), 119 (100), 99 (35), 91 (60), 71 (66). HRMS Calcd for $C_{12}H_{14}O_2$: 190.0994. Found: 190.1001.

(*E*)-3-Ethoxy-1-(4-methoxyphenyl)prop-2-en-1-one (**4c**): A colorless liquid, bp 125 °C/0.1 mmHg. ^{1}H-NMR ($CDCl_3$): 1.38 (3H, t, J=7 Hz), 3.83 (3H, s), 4.07 (2H, q, J=7 Hz), 6.37 (1H, d, J=11 Hz), 6.93 (2H, d, J=9 Hz), 7.67 (1H, d, J=11 Hz), 7.80 (2H, d, J=9 Hz). IR ($CHCl_3$) cm^{-1}: 1662. MS *m/z* (relative intensity): 206 (M^+, 21), 191 (4), 177 (11), 162 (22), 135 (100), 107 (10), 99 (10), 71 (23). HRMS Calcd for $C_{12}H_{14}O_3$: 206.943. Found: 206.0948.

(*E*)-4-(3-Ethoxy-1-oxoprop-2-en-1-yl)acetanilide (**4d**): A viscous liquid. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7 Hz), 2.20 (3H, s), 4.08 (2H, q, J=7 Hz), 6.43 (1H, d, J=12 Hz), 7.6—7.9 (5H, m), 9.00—9.20 (1H, br). IR ($CHCl_3$) cm^{-1}: 1698, 1660, 1520. MS *m/z* (relative intensity): 233 (M^+, 12), 205 (38), 190 (5), 177 (19), 120 (100), 99 (7), 71 (20). HRMS Calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1022.

(*E*)-3-Ethoxy-1-(3-pyridinyl)prop-2-en-1-one (**7**): A colorless liquid, bp 140—150 °C/0.7 mmHg. Yield 44%. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, J=6 Hz), 4.10 (2H, q, J=6 Hz), 6.40 (1H, d, J=12 Hz), 7.43 (1H, dd,

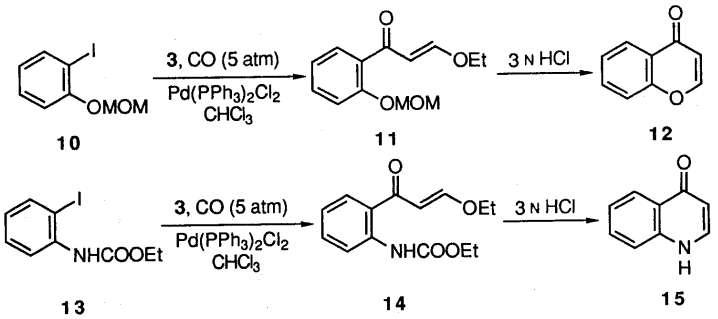


Chart 4

$J=8$, 4 Hz), 7.83 (1H, d, $J=12$ Hz), 8.21 (1H, dd, $J=8$, 2 Hz), 8.75 (1H, dd, $J=4$, 2 Hz), 9.13 (1H, d, $J=2$ Hz). IR ($CHCl_3$) cm^{-1}: 1665. MS *m/z* (relative intensity): 177 (M^+, 14), 149 (33), 134 (29), 160 (50), 99 (42), 78 (37), 71 (100). HRMS Calcd for $C_{10}H_{11}NO_2$: 177.0789. Found: 177.0790.

(*E*)-3-Ethoxy-1-(2-methoxymethoxyphenyl)prop-2-en-1-one (**11**): A yellow viscous liquid. Yield 50%. ^{1}H-NMR ($CDCl_3$): 1.32 (3H, t, $J=7$ Hz), 3.43 (3H, s), 3.95 (2H, q, $J=7$ Hz), 5.15 (2H, s), 6.17 (1H, d, $J=14$ Hz), 7.0—7.6 (4H, m), 7.50 (1H, d, $J=14$ Hz). IR ($CHCl_3$) cm^{-1}: 1658. MS *m/z* (relative intensity): 236 (M^+, 5), 205 (11), 191 (100), 175 (16), 161 (42), 147 (23), 121 (34), 99 (3), 71 (22). HRMS Calcd for $C_{13}H_{16}O_4$: 236.1049. Found: 236.1055.

Ethyl (*E*)-2-(3-Ethoxy-1-oxoprop-2-en-1-yl)phenylcarbanilate (**14**): A yellow viscous liquid. Yield 56%. ^{1}H NMR ($CDCl_3$): 1.32 (3H, t, $J=6$ Hz), 1.40 (3H, t, $J=7$ Hz), 4.10 (2H, q, $J=6$ Hz), 4.23 (2H, q, $J=7$ Hz), 6.12 (1H, d, $J=12$ Hz), 6.9—7.9 (4H, m), 8.47 (1H, d, $J=12$ Hz), 11.00—11.20 (1H, br). IR ($CHCl_3$) cm^{-1}: 1730, 1658. MS *m/z* (relative intensity): 263 (M^+, 10), 218 (61), 174 (26), 146 (100), 99 (4), 71 (16). HRMS Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1158.

Palladium-Catalyzed Carbonylative Coupling Relation of Ethyl 4-Iodobenzoate (1e) with 3 A mixture of **1e** (1.10 g, 4 mmol), **3** (1.44 g, 4 mmol), $PdCl_2(PPh_3)_2$ (100 mg), and $CHCl_3$ (25 ml) was heated under carbon monoxide (5 atm) atmosphere at 80 °C for 5 h in a sealed apparatus. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2–hexane (1 : 1) and CH_2Cl_2 as eluents. The product obtained from the CH_2Cl_2–hexane eluate was ethyl (*Z*)-4-(2-ethoxyethenyl)benzoate (**5e**) (0.23 g, 26%). The product obtained from the CH_2Cl_2 eluate was ethyl (*E*)-4-(3-ethoxy-1-oxoprop-2-en-1-yl)benzoate (**4e**) (0.59 g, 59%).

4e: A pale yellow viscous liquid. ^{1}H-NMR ($CDCl_3$): 1.37 (3H, t, $J=7$ Hz), 1.40 (3H, t, $J=7$ Hz), 4.08 (2H, q, $J=7$ Hz), 4.40 (2H, q, $J=7$ Hz), 6.37 (1H, d, $J=12$ Hz), 7.80 (1H, d, $J=12$ Hz), 7.95 (2H, d, $J=6$ Hz), 8.13 (2H, d, $J=6$ Hz). IR ($CHCl_3$) cm^{-1}: 1710, 1659. MS *m/z* (relative intensity): 248 (M^+, 83), 219 (45), 191 (19), 177 (51), 131 (68), 99 (94), 71 (100). HRMS Calcd for $C_{14}H_{16}NO_4$: 248.1049. Found: 248.1053.

5e: A colorless liquid; bp 150 °C/3 mmHg (lit.[2]) bp 150 °C/3 mmHg). ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, $J=7$ Hz), 1.36 (3H, t, $J=7$ Hz), 4.00 (2H, q, $J=7$ Hz), 4.36 (2H, q, $J=7$ Hz), 5.26 (1H, d, $J=6$ Hz), 6.26 (1H, d, $J=6$ Hz), 7.66 (2H, d, $J=10$ Hz), 8.00 (2H, d, $J=10$ Hz). IR ($CHCl_3$) cm^{-1}: 1715, 1280, 1105.

Palladium-Catalyzed Carbonylative Coupling Reaction of 4-Nitroiodobenzene (1f) with 3 According to the above procedure, (*Z*)-1-(2-ethoxyethenyl)-4-nitrobenzene (**5f**) (0.31 g, 40%) and (*E*)-3-ethoxy-1-(4-nitrophenyl)prop-2-en-1-one (**4f**) (0.22 g, 25%) were obtained from the reaction of **1f** (1.01 g, 4 mmol), **3** (1.44 g, 4 mmol), $PdCl_2(PPh_3)_2$ (100 mg), and $CHCl_3$ (20 ml) under a carbon monoxide (5 atm) atmosphere at 80 °C for 5 h.

4f: Yellow prisms (hexane), mp 81.5—82 °C. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, $J=7$ Hz), 4.15 (2H, q, $J=7$ Hz), 6.42 (1H, d, $J=12$ Hz), 7.87 (1H, d, $J=12$ Hz), 8.03 (2H, d, $J=10$ Hz), 8.30 (2H, d, $J=10$ Hz). IR ($CHCl_3$) cm^{-1}: 1662, 1520, 1340. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.93; H, 4.89; N, 6.39.

5f: A colorless liquid, bp 140—150 °C/3 mmHg (lit.[2]) bp 140—150 °C/3 mmHg). ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, $J=8$ Hz), 4.07 (2H, q, $J=8$ Hz), 5.30 (1H, d, $J=7$ Hz), 6.40 (1H, d, $J=7$ Hz), 7.66 (2H, d, $J=9$ Hz), 8.13 (2H, d, $J=9$ Hz). IR ($CHCl_3$) cm^{-1}: 1510, 1345.

Palladium-Catalyzed Carbonylative Coupling Reaction of 2-Halopyridine (8a, b) with 3 a) From 2-Iodopyridine (**8a**): According to the general procedure, a mixture of **8a** (0.95 g, 6 mmol), **3** (2.16 g, 6 mmol) $PdCl_2(PPh_3)_2$ (210 mg), and $CHCl_3$ (10 ml) was heated under a carbon monoxide (5 atm) atmosphere for 10 h to give (*Z*)-2-(2-ethoxyethenyl)pyridine (**9**) (120 mg, 32%) as a colorless liquid, bp 80 °C/3 mmHg (lit.[2]) bp 80 °C/3 mmHg). ^{1}H-NMR ($CDCl_3$): 1.32 (3H, t, $J=7$ Hz), 3.97 (2H, q, $J=7$ Hz), 5.55 (1H, d, $J=7$ Hz), 6.40 (1H, d, $J=7$ Hz), 7.33 (1H, dd, $J=4$, 1 Hz), 7.5—8.1 (2H, m), 8.48 (1H, dd, $J=3$, 1 Hz).

b) From 2-Bromopyridine (**8b**): According to the general procedure, a mixture of **8b** (0.51 g, 2.5 mmol), **3** (0.90 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (90 mg), and $CHCl_3$ (10 ml) was heated under a carbon monoxide (5 atm) atmosphere for 4 h to give **9** (90 mg, 8%) as a colorless liquid.

Chromone (12) A mixture of **11** (0.50 g, 2.1 mmol) and 3 N HCl (10 ml) was refluxed for 1 h. After cooling, the mixture was neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from H_2O to give **12** as colorless scales (0.20 g, 65%), mp 56—57 °C (lit.[8] mp 59 °C). ^{1}H-NMR ($CDCl_3$): 6.40 (1H, d, $J=6$ Hz), 7.3—7.8 (4H, m), 7.81 (1H, d, $J=6$ Hz). IR ($CHCl_3$) cm^{-1}: 1653.

4(1*H*)-Quinolinone (15) By the same procedure as used for the preparation of **12**, **15** (0.18 g, 65%) was obtained from the reaction of **14** (0.50 g, 1.9 mmol) with 3 N HCl (10 ml) as colorless needles (EtOH), mp 238—240 °C (lit.[9] mp 238—239 °C). ^{1}H-NMR (DMSO-d_6/DSS): 6.13 (1H, d, $J=7$ Hz), 7.3—7.8 (3H, m), 7.98 (1H, d, $J=8$ Hz), 8.1—8.3 (1H, m), 11.80—12.10 (1H, br). IR ($CHCl_3$) cm^{-1}: 3060, 1640, 1510.

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