A One-Pot Palladium-Catalyzed Synthesis of β,β-Diarylketones and Aldehydes from Aryl Iodides and α,β-Unsaturated Carbonyl Compounds

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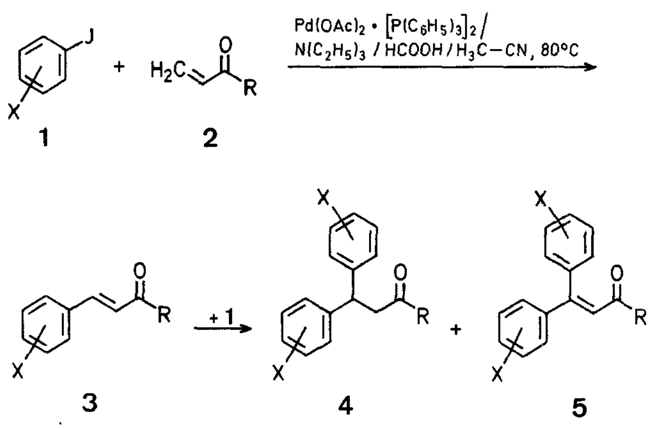
The palladium-catalyzed conjugate addition type reaction of aryl iodides to α,β-unsaturated carbonyl compounds[1] appears to provide a useful alternative to the previously reported palladium-catalyzed addition of arylmercury compounds[2].

As part of a program devoted to establish the full scope of the reaction, we describe a new application concerning a one-pot synthesis of β,β-diarylketones and β,β-diarylaldehydes from aryl iodides **1** and butenone, 1-penten-3-one, or propenal (**2a–c**, respectively) in the presence of a palladium catalyst.



1	X		X
a	H	e	4-NH_2
b	4-CH_3	f	4-NH–COO–CH_2–C_6H_5
c	4-OH	g	4-NH–CO–CH_3
d	4-OCH_3	h	3-NH–CO–CH_3
		i	3-CH_2OH

2	R
a	CH_3
b	C_2H_5
c	H

The reaction proceeds through a palladium-catalyzed vinylic substitution[3] on the β-unsubstituted α,β-unsaturated carbonyl compounds **2** followed by an *in situ* conjugate addition type reaction on the β-substituted α,β-unsaturated carbonyl compounds **3** to give **4**. Compounds **5**, derived from a double vinylic substitution reaction, are also isolated in variable amounts. Furthermore, arenes and biaryls derived from palladium-catalyzed reduction[4] and coupling[5] of aryl iodides are found. Clearly, these competitive reactions lower the amount of the aryl iodide available for the vinylic substitution/conjugate addition sequence and make it necessary to use the aryl iodide in relatively large excess.

Therefore, reactions have been carried out by reacting the α,β-unsaturated carbonyl compound **2** (3.56 mmol) with an arbitrary 500 mol % of the aryl iodide **1** in the presence of triethylamine (700 mol %), formic acid (600 mol %), bis[triphenylphosphine]palladium diacetate (2 mol %), and acetonitrile (1 ml). The reaction mixture has been maintained at 80°C for an appropriate period and worked-up. Pure products have been obtained through open-column chromatography.

The results are summarized in Table 1. In favourable cases, the excess of the expensive aryl iodide and the amount of catalyst can be lowered. Thus, the reaction of 4-methoxyphenyl iodide (**1d**) with 1-penten-3-one (**2b**; 17.83 mmol) gives satisfactory results (67 % **4db**; 18 % **5db**) under the following conditions: 80°C, 8 h, 350 mol % **1d**, 700 mol % triethylamine, 600 mol % formic acid, and 1 mol % palladium catalyst in acetonitrate (5 ml).

Generally, our procedure affords good yields of compounds **4** and represents a convenient entry into this class of compounds. Only in the presence of free amino and hydroxy groups are unsatisfactory results obtained (see Table 1).

Table 1. Palladium-Catalyzed Reaction of Aryl Iodides **1** and α,β-Unsaturated Carbonyl Compounds **2**

Aryl Iodide **1**	α,β-Unsaturated Carbonyl Compound **2**	Reaction time [h]	Yield [%][a] **3**	**4**	**5**
1a	**2a**	12	5	72	7
1b	**2a**	12	7	74	–
1c	**2a**	7	–	52[b]	28[b]
1d	**2a**	8	4	75	–
1e	**2a**	6	–	15[c]	46[c]
1f	**2a**	15	–	60	16
1g	**2a**	15	–	70	–
1h	**2a**	13	–	73	–
1a	**2b**	13	–	72	–
1c	**2b**	7	–	31[b]	50[b]
1d	**2b**	5	–	71	20
1h	**2b**	13	6	71	–
1i	**2b**	12	5	71	–
1b	**2c**	15	–	48	–
1c	**2c**	10	–	–	73
1d	**2c**	10	–	64	–

[a] Isolated yields calculated for starting compounds **2**. Yields refer to single, not optimized runs.

[b] Yields of isolated acetyl derivatives obtained by treatment of the reaction mixture of **4ca** and **5ca** with acetyl chloride.

[c] Compounds **4ea** and **5ea** are obtained as a mixture of the corresponding hydrobromides. Composition determined by ^1H-N.M.R. analysis.

Melting points are uncorrected and were determined with a Büchi apparatus.

All reagents are commercially available and were used without further purification. Aryl iodides **1f**, **g**, **h** were prepared from commercially available compounds by standard methods. The catalyst was purchased from Fluka.

4,4-Diarylbutan-2-ones, 5,5-Diarylpentan-3-ones, and 3,3-Diarylpropanals (4); General Procedure:

Bis[triphenylphosphine]palladium diacetate (0.15 g, 0.2 mmol) and acetonitrile (3 ml) are added to a mixture of the starting α,β-unsaturated carbonyl compound **2** (10 mmol), aryl iodide **1** (50.0 mmol), and triethylamine (7.08 g, 70.0 mmol). Formic acid (2.76 g, 60.0 mmol) is slowly added with cooling (ice bath). The mixture is then purged with argon and stirred at 80°C under argon, the reflux condenser being connected to a mercury valve. After an appropriate period, the mixture is diluted with dichloromethane (300 ml) and washed with water (3 × 300 ml). The organic layer is separated, dried with magnesium sulfate, and concentrated at reduced pressure to give a residue which is purified through open-column chromatography (silica gel, Merck, 70–230 mesh; eluent: cyclohexane/ethyl acetate mixtures).

Table 2. Characterization of Compounds **3**, **4**, and **5** prepared

Product	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R.[b] ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$)[c] δ [ppm]
3ba	oil	30°[6]	1665, 1610, 1260, 980, 805	7.52 (d, J = 16.5 Hz, 1H); 7.34 (AA'BB', J = 7.6 Hz, 4H); 6.69 (d, J = 16.5 Hz, 1H); 2.37 (s, 3H); 2.35 (s, 3H)
3da	68–70°	74–75°[7]	1680, 1590, 1260, 990, 820	7.46 (d, J = 16.5 Hz, 1H); 7.18 (AA'BB', J = 9.0 Hz, 4H); 6.57 (d, J = 16.5 Hz, 1H); 3.80 (s, 3H); 2.33 (s, 3H)
3hb	119–120°	$C_{13}H_{15}NO_2$ (217.3)	3300, 1670, 1590, 1120, 1040, 805	8.80 (br. s, 1H); 7.93–7.20 (m, 4H); 7.50 (d, J = 16.5 Hz, 1H); 6.70 (d, J = 16.5 Hz, 1H); 2.65 (q, J = 7.3 Hz, 2H); 2.20 (s, 3H); 1.13 (t, J = 7.3 Hz, 3H)
3ib	165–166°[d]	$C_{12}H_{14}O_2$ (190.2)	3410, 1655, 1610, 1200, 1045, 805	7.49 (d, J = 16.5 Hz, 1H); 7.55–7.25 (m, 4H); 6.67 (d, J = 16.5 Hz, 1H); 4.63 (br. s, 2H); 4.43 (br. s, 1H); 2.60 (q, J = 7.3 Hz, 2H); 1.10 (t, J = 7.3 Hz, 3H)
4aa	179–180°[d]	$C_{16}H_{16}O$ (224.3)	1715, 1600, 1495, 1160, 750, 700	7.50–7.03 (m, 10H); 4.60 (t, J = 7.5 Hz, 1H); 3.15 (d, J = 7.5 Hz, 2H); 2.02 (s, 3H)
4ba	72–73°[d]	$C_{18}H_{20}O$ (252.3)	1705, 1510, 1020, 805, 765, 740	7.10 (s, 8H); 4.51 (t, J = 7.6 Hz, 1H); 3.12 (d, J = 7.6 Hz, 2H); 2.27 (s, 6H); 2.03 (s, 3H)
4ca[e]	99–100°	$C_{20}H_{20}O_5$ (340.4)	1760, 1710, 1200, 1170, 915, 855	7.10 (AA'BB', J = 9.0 Hz, 8H); 4.58 (t, J = 7.5 Hz, 1H); 3.11 (d, J = 7.5 Hz, 2H); 2.20 (s, 6H); 2.03 (s, 3H)
4da	158–159°[d]	$C_{18}H_{20}O_3$ (284.3)	1710, 1510, 1250, 1180, 1035, 825	6.97 (AA'BB', J = 9.0 Hz, 8H); 4.47 (t, J = 7.6 Hz, 1H); 3.70 (s, 6H); 3.08 (d, J = 7.6 Hz, 2H); 2.03 (s, 3H)
4ea ·2HBr[f]	280–290°	$C_{16}H_{20}Br_2N_2O$ (416.1)	2560, 1700, 1505, 1170, 1020, 815	9.40 (br. s, 6H); 7.37 (AA'BB', J = 9.0 Hz, 8H); 4.60 (t, J = 7.5 Hz, 1H); 3.25 (d, J = 7.5 Hz, 2H); 2.12 (s, 3H)[g]
4fa	136–137°	$C_{32}H_{30}N_2O_5$ (522.6)	3330, 1695, 1525, 1240, 1060, 740	7.45–6.95 (m, 20H); 5.13 (s, 4H); 4.45 (t, J = 7.6 Hz, 1H); 3.03 (d, J = 7.6 Hz, 2H); 2.00 (s, 3H)
4ga	186–187°	$C_{20}H_{22}N_2O_3$ (338.4)	3300, 1700, 1660, 1520, 815	9.87 (br. s, 2H); 7.37 (AA'BB', J = 7.5 Hz, 8H); 4.40 (t, J = 7.6 Hz, 1H); 3.19 (d, J = 7.6 Hz, 2H); 2.03 (m, 9H)
4ha	233–234°	$C_{20}H_{22}N_2O_3$ (338.4)	3280, 1715, 1670, 1550, 1170, 800	9.85 (br. s, 2H); 7.55–6.87 (m, 8H); 4.40 (t, J = 7.5 Hz, 1H); 3.17 (d, J = 7.5 Hz, 2H); 2.10 (s, 3H); 2.02 (s, 6H)
4ab	156–157°[d]	37–38°[8]	1715, 1600, 1495, 1115, 750, 700	7.40–7.00 (m, 10H); 4.60 (t, J = 7.8 Hz, 1H); 3.12 (d, J = 7.8 Hz, 2H); 2.30 (q, J = 7.4 Hz, 2H); 0.91 (t, J = 7.4 Hz, 3H)
4cb[e]	112–113°	$C_{21}H_{22}O_5$ (354.4)	1760, 1710, 1205, 1170, 915, 850	7.08 (AA'BB', J = 8.1 Hz, 8H); 4.60 (t, J = 7.5 Hz, 1H); 3.07 (d, J = 7.5 Hz, 2H); 2.28 (q, J = 7.5 Hz, 2H); 2.15 (s, 6H); 0.90 (t, J = 7.5 Hz, 3H)
4db	95–96°[d]	$C_{19}H_{22}O_3$ (298.4)	1710, 1600, 1250, 1035, 830	6.97 (AA'BB', J = 9.0 Hz, 8H); 4.50 (t, J = 7.6 Hz, 1H); 3.67 (s, 6H); 3.03 (d, J = 7.6 Hz, 2H); 2.27 (q, J = 7.4 Hz, 2H); 0.90 (t, J = 7.4 Hz, 3H)
4hb	179–180°	$C_{21}H_{24}N_2O_3$ (352.4)	3305, 1710, 1665, 1545, 1270, 715	9.90 (br. s, 2H); 7.60–6.88 (m, 8H); 4.40 (t, J = 7.6 Hz, 1H); 3.15 (d, J = 7.6 Hz, 2H); 2.43 (q, J = 7.3 Hz, 2H); 2.02 (s, 6H); 0.85 (t, J = 7.3 Hz, 3H)
4ib	124–125°[d]	$C_{19}H_{22}O_3$ (298.4)	3390, 1705, 1020, 795, 705	7.33–6.93 (m, 8H); 4.50 (t, J = 7.6 Hz, 1H); 4.35 (s, 4H); 4.06 (br. s, 2H); 3.07 (d, J = 7.6 Hz, 2H); 2.23 (q, J = 7.3 Hz, 2H); 0.80 (t, J = 7.3 Hz, 3H)
4bc	75–78°	$C_{17}H_{18}O$ (238.3)	1725, 1600, 1510, 1175, 810	9.70 (t, J = 2.2 Hz, 1H); 7.25–6.95 (m, 8H); 4.51 (t, J = 7.9 Hz, 1H); 3.07 (dd, J = 7.9 Hz, 2.2 Hz, 2H); 2.28 (s, 6H)
4dc	83–85°	$C_{17}H_{18}O_3$ (270.3)	1725, 1600, 1250, 1150, 830	9.65 (t, J = 2.1 Hz, 1H); 6.95 (AA'BB', J = 9.0 Hz, 8H); 4.47 (t, J = 7.6 Hz, 1H); 3.65 (s, 6H); 3.00 (dd, J = 7.6 Hz, 2.1 Hz, 2H)
5aa	152–154°[d]	153–154°[d, 9]	1695, 1590, 1490, 780, 765, 700	7.50–7.10 (m, 10H); 6.43 (s, 1H); 1.73 (s, 3H)
5ca[e]	158–159°[d]	$C_{20}H_{18}O_5$ (338.3)	1760, 1655, 1200, 1170, 915, 850	7.40–6.97 (m, 8H); 6.57 (s, 1H); 6.26 (s, 3H); 6.23 (s, 3H); 1.90 (s, 3H)
5fa	142–143°	$C_{32}H_{28}N_2O_5$ (520.6)	3300, 1740, 1700, 1640, 1240, 740	7.55–7.00 (m, 20H); 6.50 (s, 1H); 5.18 (s, 4H); 1.88 (s, 3H)
5cb[e]	107–108°	$C_{21}H_{20}O_5$ (352.4)	1760, 1685, 1200, 1170, 910, 850	7.40–6.97 (m, 8H); 6.57 (s, 1H); 2.29 (q, J = 7.5 Hz, 2H); 2.23 (s, 3H); 2.21 (s, 3H); 0.95 (t, J = 7.5 Hz, 3H)
5db	139–140°[d]	$C_{19}H_{20}O_3$ (296.3)	1650, 1510, 1250, 1035, 835	7.33–6.70 (m, 8H); 6.48 (s, 1H); 3.83 (s, 3H); 3.80 (s, 3H); 2.27 (q, J = 7.4 Hz, 2H); 0.98 (t, J = 7.4 Hz, 3H)
5cc	138–140°	$C_{15}H_{12}O_3$ (240.2)	3300,1630, 1600, 1235, 1175, 840	9.37 (d, J = 8.2 Hz, 1H); 7.37–6.73 (m, 8H); 6.43 (d, J = 8.2 Hz, 1H); 4.90 (br. s, 2H)

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.41, N ±0.36.

[b] Determined on a Perkin Elmer-297 spectrometer in Nujol; except **3ba** which has been measured as liquid film.

[c] Measured on a Varian EM 390 spectrometer.

[d] m.p. of the 2,4-dinitrophenyl hydrazone derivative.

[e] Isolated and characterized as acetyl derivative.

[f] Hydrobromide obtained by treatment of **4fa** with 37% hydrobromic acid in acetic acid.

[g] Measured in DMSO-d_6.

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