A Facile Approach to Arylacetaldehydes via Polymeric Palladium Catalyst

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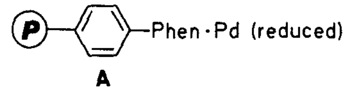
Several arylacetaldehydes **5** were synthesized in moderate yields via Heck reaction of acrylamide (**1**) with substituted iodobenzenes **2** in the presence of the polymeric catalyst Ⓟ-phenyl-(1,10-phenanthroline)-palladium(0) [Ⓟ-ph-phen.Pd(0)] followed by Hofmann reaction and subsequent hydrolysis.

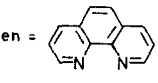
Arylacetaldehydes are important substances for organic synthesis. A number of methods have been reported for the syntheses of these aldehydes, e.g., the oxidation of 2-phenylethanol,[1,2] the reduction of phenylacetic acid,[3] benzylcyanide[4] or 2-nitrostyrene.[5] Some methods are unsuitable for preparative purposes because of the poor yield, and some methods suffer from the problem that the starting material is not readily available. We describe here a facile synthetic route to these kind of compounds. Our approach is based on the Heck reaction of acrylamide with iodobenzene in the presence of a polymeric palladium catalyst, followed by Hofmann reaction and subsequent hydrolysis.

We[6] have treated iodobenzene with acrylamide under the traditional Heck reaction conditions by using tributylamine as the base and palladium acetate as the catalyst, however, the catalyst was gradually aggregated to an inactive palladium black, resulting in a poor yield of product. Recently we[6] described a polymer-bound palladium catalyst Ⓟ-ph-phen.Pd (reduced) **A**.



A

phen =



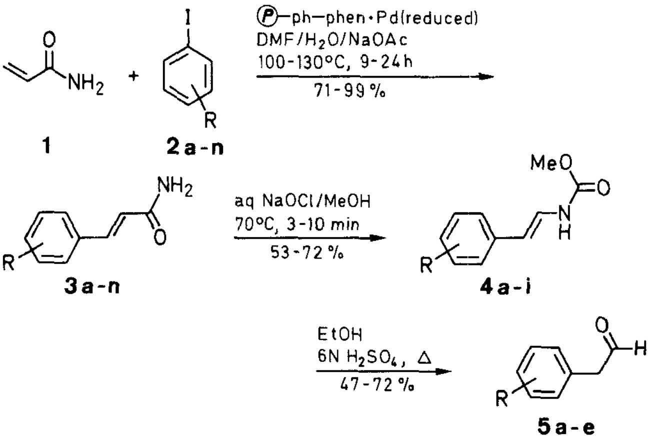
It showed high activity for the Heck reaction of olefins with substituted iodobenzenes by using tributylamine as the base. When it was used for the reaction of iodobenzene with acrylamide, (*E*)-cinnamamide was obtained in good yield (80%). Unfortunately, an extensive loss of catalytic activity was observed after several cycles due to the palladium leaching from polymer support. We found that this is mainly caused by the competitive complexation of tributylamine existing in reaction media towards the metal. In a continuous study,[7] we found when sodium acetate and dimethylformamide were used in place of tributylamine, catalyst **A** could be recovered and re-used for the above reaction in high yields. Even after recycling up to ten-times there was no decrease in activity. With this system and in the presence of catalyst **A**, a variety of substituted iodobenzenes **2** were reacted with acrylamide (**1**) to give the cinnamamide derivatives **3** in good to excellent yields (Scheme). In all reactions 0.32 mol% catalyst based on the aryl iodide was used. The results are summarized in Table 1. Generally, the reaction was carried out at 100 °C. 4-Iodoanisole (**2h**), 4'-iodoacetophenone (**2k**) and 4-iodobenzoic acid (**2j**) required a temperature of 130 °C. Andersson and coworkers[18] indicated that polymeric catalysts tend to be more efficient in the Heck reaction. In our case, when 2,3,4-trimethoxy-1-iodobenzene (**2m**) was used, no reaction could be observed with palladium(II) acetate as catalyst, even after heating at 130 °C for 24 hours. However, with the polymeric catalyst **A**, the reaction proceeded smoothly at 130 °C to give the desired product in good yield. It appeared that this polymeric catalyst is sometimes more active than the homogeneous species from which it is derived.

Table 1. Cinnamamides 3 Prepared

Product	Reaction Temp. (°C)/ Time (h)	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp. (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ, J (Hz)
3a	100/3	82	144	147–148[8]	3374, 3162, 1662, 1607, 969, 758, 699	6.72 (d, 1H, J = 15.9, CH=), 7.33–7.66 (m, 6H, ArH, CH=)
3b	100/9	93	212	201[9]	3340, 3155, 1673, 1089, 989, 826	6.67 (d, 1H, J = 15.9, CH=), 7.37–7.68 (m, 5H, ArH, CH=)
3c	100/11	98	214	215–216.5[10]	3322, 3155, 1672, 1068, 988, 823	6.67 (d, 1H, J = 15.9, CH=), 7.35–7.66 (m, 5H, ArH, CH=)
3d	100/8	85	166	168[11]	3348, 3171, 1667, 1054, 966, 752	6.73 (d, 1H, J = 15.1, CH=), 7.39–8.01 (m, 5H, ArH, CH=)
3e	120/9	87	164	$C_9H_7Cl_2NO$ (216.1)	3374, 3192, 1667, 980, 776, 729	6.77 (d, 1H, J = 15.9, CH=), 7.25–7.53 (m, 4H, ArH, CH=)
3f	100/12	88	216	217[12]	3379, 3176, 1666, 1520, 1342, 980	6.89 (d, 1H, J = 16.0, CH=), 7.53–8.30 (m, 5H, ArH, CH=)
3g	100/8	90	192	189–190[12]	3323, 3147, 1668, 1391, 990, 815	2.33 (s, 3H, Me), 6.61 (d, 1H, J = 16.0, CH=), 7.17–7.54 (m, 5H, ArH, CH=)
3h	130/12	86	195	186[14]	3346, 3186, 1663, 1254, 1016, 989, 829	3.82 (s, 3H, MeO), 6.53 (d, 1H, J = 15.9, CH=), 6.94–7.60 (m, 5H, ArH, CH=)
3i	100/8	88	197	195–196[12]	3450, 3150, 1702, 1520, 1356, 972	6.82 (d, 1H, J = 15.8, CH=), 7.47–8.39 (m, 5H, ArH, CH=)
3j	130/9	71	308	$C_{10}H_9NO_3$ (191.2)	3357, 3159, 2525–3159 (br), 1688, 1637, 977, 962, 841	6.75 (d, 1H, J = 15.9, CH=), 7.42–8.04 (m, 5H, ArH, CH=)
3k	130/8	82	202	$C_{11}H_{11}NO_2$ (189.2)	3391, 3165, 1668 (br), 979, 824	2.61 (s, 3H, MeCO), 6.76 (d, 1H, J = 16.0, CH=)
3l	130/12	90	166	164–166[15]	3334, 3140, 1668, 1390, 1267, 1024, 991, 856, 806	3.83 (s, 6H, MeO), 6.53 (d, 1H, J = 15.8, CH=), 7.05–7.52 (m, 4H, ArH, CH=), 7.42–8.06 (m, 5H, ArH, CH=)
3m	130/24	88	163	169[16]	3394, 3153, 1678, 1383, 1271, 1093, 950, 806	3.78 (s, 3H, MeO), 3.82 (s, 3H, MeO), 3.83 (s, 3H, MeO), 6.53 (d, 1H, J = 15.7, CH=), 7.23–7.62 (m, 3H, ArH, CH=)
3n	130/12	99	182	184–185[17]	3365, 3166, 2888, 1659, 1447, 1256, 1036, 858, 817	6.08 (s, 2H, OCH_2O), 6.47 (d, 1H, J = 15.8, CH=), 6.99–7.47 (m, 4H, ArH, CH=)

[a] Yield of isolated product **3** based on **2**.

[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.2, N ±0.2.



2–5	R	2–5	R
a	H	**h**	4-MeO
b	4-Cl	**i**	3-O_2N
c	4-Br	**j**	4-HO_2C
d	2-Cl	**k**	4-Ac
e	2,6-Cl_2	**l**	3,4-$(MeO)_2$
f	4-O_2N	**m**	2,3,4-$(MeO)_3$
g	4-Me	**n**	3,4-methylenedioxy

Scheme

In the Hofmann reaction, an unsubstituted amide is converted to a primary amine with one less carbon atom by treatment with bromine (or chlorine) and alkali. However, α,β-unsaturated amides usually give carbamates when treated with methanolic sodium hypochlorite.[15] Cinnamamides **3a–i** prepared above were subjected to Hofmann reaction (Scheme). The conversion of these compounds to carbamates occurred very rapidly, when the amides **3a–i** in methanolic solution were treated with an equimolar amount of sodium hypochlorite on a water bath for several minutes, a thick sludge of carbamate crystals **4a–i** would form soon after cooling (Table 2). In the IR spectra of these products, a strong band appeared at the region of 935–957 cm^{-1}, and in the ^{1}H-NMR spectra, the coupling constants of the adjacent olefinic hydrogens were between J = 14.63 to 14.97 Hz. All these data were consistent with the (*E*)-structure.

These carbamates were readily hydrolyzed to give the corresponding aldehydes. When dilute sulfuric acid was gradually added to an ethanolic solution of the methyl carbamates **4a–e**, aldehydes **5a–e** would be distilled out with steam in moderate yields[20] (Scheme) (Table 3).

Table 2. Methyl Carbamates **4** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp. (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR (acetone-d_6) δ, *J* (Hz)
4a	8	62	120–121	122[12]	3302, 1736, 1705, 1663, 951, 751, 693	3.69 (s, 3H, CO_2Me), 6.15 (d, 1H, *J* = 15.0, CH=), 7.19–7.25 (m, 6H, ArH, CH=)
4b	8	66	127	$C_{10}H_{10}ClNO_2$ (211.6)	3335, 2950, 1709, 1656, 1059, 936, 810	3.69 (s, 3H, CO_2Me), 6.10 (d, 1H, *J* = 14.7, CH=), 7.17–7.42 (m, 5H, ArH, CH=), 8.12 (br, NH)
4c	5	72	130	$C_{10}H_{10}BrNO_2$ (256.1)	3317, 2946, 1700, 1663, 1065, 937, 807	3.86 (s, 3H, CO_2Me), 6.09 (d, 1H, *J* = 14.7, CH=), 7.17–7.46 (m, 5H, ArH, CH=), 8.80 (br, NH)
4d	5	60	122	$C_{10}H_{10}ClNO_2$ (211.6)	3290, 2951, 1734, 1702, 1661, 955	3.70 (s, 3H, CO_2Me), 6.45 (d, 1H, *J* = 14.6, CH=), 7.19–7.62 (m, 5H, ArH, C=), 8.88 (br, NH)
4e	8	63	124	$C_{10}H_9Cl_2NO_2$ (246.1)	3313, 2949, 1699, 1666, 982	3.70 (s, 3H, CO_2Me), 6.48 (d, 1H, *J* = 14.6, CH=), 7.15–7.40 (m, 4H, ArH, CH=), 8.40 (br, NH)
4f	10	60	188	188[12]	3311, 2956, 1705, 1653, 1502, 1348, 946	3.72 (s, 3H, CO_2Me), 6.24 (d, 1H, *J* = 14.6, CH=), 7.42–8.18 (m, 5H, ArH, CH=), 9.18 (br, NH)
4g	6	63	125	$C_{11}H_{13}NO_2$ (191.2)	3313, 2949, 1708, 1658, 958, 805	2.25 (s, 3H, Ar$\underline{Me}$), 3.68 (s, 3H, CO_2Me), 6.10 (d, 1H, *J* = 14.7, CH=), 7.09–7.25 (m, 5H, ArH, CH=)
4h	3	62	134	135[19]	3327, 2940, 2837, 1719, 1699, 1662, 1287, 953, 811	3.67 (s, 3H, CO_2Me), 3.74 (s, 3H, ArO$\underline{Me}$), 6.08, (d, 1H, *J* = 14.8, CH=), 6.76–7.28 (m, 5H, ArH, CH=)
4j	6	53	139	140[12]	3309, 2959, 1706, 1662, 945	3.71 (s, 3H, CO_2Me), 6.23 (d, 1H, *J* = 14.7, CH=), 7.33–8.07 (m, 5H, ArH, CH=), 8.99 (br, NH)

[a] Yield of isolated product **4** based on **3**.

[b] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.1.

Table 3. Arylacetaldehydes **5** Prepared

Product	Yield[a] (%)	bp (°C)/mbar or mp (°C)	Molecular Formula[b] or Lit. data (°C)	IR (Nujol) ν (cm^{-1})	^{1}H-NMR (acetone-d_6/TMS) δ, *J* (Hz)
5a	72	55–56/3	78/13.3[12]	2828, 2728, 1726, 750, 701	3.68 (d, 2H, CH_2), 7.28 (s, 5H, ArH), 9.68 (t, 1H, CHO)
5b	47	106–107/6 40-1	104–106/13.3[21] 39–40[22]	2848, 2743, 1702	3.75 (d, 2H, CH_2), 7.18–7.31 (m, 4H, ArH), 9.70 (t, 1H, CHO)
5c	49	113–114/7	122–125/16[10]	2843, 2738, 1725, 1702	3.72 (d, 2H, CH_2), 7.12–7.55 (m, 4H, ArH), 9.72 (t, 1H, CHO)
5d	50	88–89/3	C_8H_7ClO (154.6)	2828, 2730, 1725	3.88 (d, 2H, CH_2), 7.27–7.38 (m, 4H, ArH), 9.73 (t, 1H, CHO)
5e	60	101/3 69	$C_8H_6Cl_2O$ (189.0)	2849, 2735, 1719, 1695	4.16 (d, 2H, CH_2), 7.23–7.55 (m, 3H, ArH), 9.78 (t, 1H, CHO)

[a] Yield of isolated product **5** based on **4**.

[b] Satisfactory microanalyses obtained: C ±0.2, H ±0.2.

Since cinnamamides are readily available from the Heck reaction, the polymeric catalyst **A** can be recovered and re-used, and the Hofmann reaction and the subsequent hydrolysis are easily carried out, this approach represents a facile route for preparation of arylacetaldehydes using acrylamide as the starting material.

All reagents were of commercial quality from freshly opened containers. Reagent quality solvents were used without further purification. Melting points were taken with a Yanoco micro melting point apparatus and are uncorrected. IR spectra were obtained using a Nicolet FT-IR 170 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian FT-80 spectrometer. Microanalyses were obtained using a Perkin-Elmer 240 element analyzer. Catalyst **A** was prepared by the procedure described previously,[6] elemental analysis: found 5.08 % Pd. The substituted iodobenzenes **2a–j** are available from Aldrich Chemicals and the compounds **2k–n** were obtained by the literature methods.[23–25]

Cinnamamides 3; General Procedure:

A mixture of acrylamide (**1**, 0.60 g, 8.5 mmol), substituted iodobenzene (**2a–n**, 7.5 mmol), NaOAc (0.69 g, 8.5 mmol), DMF (3.5 mL), H_2O (1.5 mL), and catalyst **A** (0.05 g, 0.024 mmol%) is heated under Ar in an oil bath at an appropriate temperature (see Table 1). After stirring for the length of time specified in Table 1, the polymeric catalyst is separated from the mixture by filtration, washed with DMF, and re-used in the next run. The filtrate is poured into H_2O (100 mL), the precipitated product is isolated by suction and washed with H_2O. The crude product is recrystallized from EtOH to give **3**.

Methyl *N*-((*E*)-*β*-Styryl)carbamates 4; General Procedure:
To a well stirred mixture of crushed ice (300 g), and NaOH (50 g, 1.25 mol) in H_2O (75 mL), Cl_2 (27.5 g) is passed to give an alkaline solution of NaOCl. Cinnamamide (**3**, 10 mmol) is dissolved in hot MeOH (50 mL). After cooling, stock solution of NaOCl (13 mL, 10 mmol) is added. The temperature is quickly elevated to 70 °C, and the mixture is stirred at this temperature for the length of time specified in Table 2. After cooling, H_2O (100 mL) is added, the precipitated product is isolated by suction, and washed with H_2O. The crude product is recrystallized from EtOH to give **4**.

Arylacetaldehydes 5; General Procedure:
Carbamate **4** (10 mmol) is dissolved in hot EtOH (20 mL). After cooling, H_2SO_4 (6N, 7 mL) is gradually added. When all the H_2SO_4 has been added, the aldehyde is distilled with steam immediately. The crude product is distilled under reduced pressure to give **5**.

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