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An Efficient Palladium-Catalyzed Synthesis of Cinnamaldehydes from Acrolein Diethyl Acetal and Aryl Iodides and Bromides

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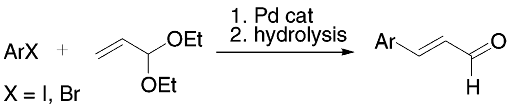
ABSTRACT



The reaction of aryl iodides and bromides with acrolein diethyl acetal in the presence of Pd(OAc)$_2$, ^{n}Bu$_4$NOAc, K$_2$CO$_3$, KCl, and DMF, at 90 °C until the disappearance of the acetal followed by the addition of 2 N HCl to the crude reaction mixture, affords cinnamaldehydes in good to high yields. A variety of functional groups are tolerated in the aryl halides, including ether, aldehyde, ketone, ester, dialkylamino, nitrile, and nitro groups. The presence of substituents close to the oxidative addition site does not hamper the reaction.

Cinnamaldehyde and its derivatives are widely used in food[1] and cosmetic[1a,1d] industries. For example, cinnamaldehyde is the main component of cassia oil as well as cinnamon bark oil and is used in flavoring compounds to impart a cinnamon flavor. Antifungal activities[2] of *trans*-cinnamaldehyde derivatives as well as their antibacterial[3] and antitermitic[4] activities were also investigated. *p*-Dialkylaminocinnamaldehydes are important compounds for nonlinear optics[5] and titration of active aldehyde dehydrogenases.[6]

The palladium-catalyzed vinylic substitution of acrolein with aryl halides would represent a useful and straighforward approach to this class of compounds. Indeed, there has been a report by Jeffery wherein phenyl, *m*-tolyl, and *p*-chlorophenyl iodides were treated with acrolein, Pd(OAc)$_2$, ^{n}BuN$_4$Cl, and NaHCO$_3$ in DMF at 20 °C for 60 h to yield the corresponding cinnamaldehydes in high yields.[7] The reaction, however, requires long reaction times, and in some cases, the desired products are obtained in low yield.[8,9]

Furthermore, formation of cinnamaldehydes from aryl bromides, which would greatly widen the scope of the synthetic procedure, still remains a challenge. At the required elevated temperatures, under basic conditions, the unsaturated carbonyl compound appears to undergo extensive polymer-

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(1) (a) Wijesekera, R. O. Historical Overview of the Cinnamon Industry. In *CRC Critical Reviews in Food Science and Nutrition* **1978**, *10*, 1−30. (b) Sato, M.; Nagane, Y.; Kawasaki, T. Ger. Offen DE 3003096, 1980; *Chem. Abstr.* **1981**, *94*, 29060. (c) Fang, J. M.; Chen, S. A.; Cheng, Y. S. *J. Agric. Food Chem.* **1989**, *37*, 744. (d) Yamada, N.; Matsubara, S. JP Patent 05179283, 1993; *Chem. Abstr.* **1994**, *120*, 14902.

(2) (a) Ishida, S.; Matsuda, A.; Kawamura, Y.; Yamanaka, K. *Chemotherapy* **1960**, *8*, 157. (b) Ferhout, H.; Bohatier, J.; Guillot, J.; Chalchat, J. C. *J. Essent. Oil Res.* **1999**, *11*, 119.

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(4) Chang, S.-T.; Cheng, S.-S. *J. Agric. Food Chem.* **2002**, *50*, 1389.

(5) For some recent references, see for example: (a) Schmalzlin, E.; Bitterer, U.; Langhals, H.; Brauchle, C.; Meerholz, K. *Chem. Phys.* **1999**, *245*, 73. (b) Tretiak, S.; Chernyak, V.; Mukamel, S. *Chem. Phys.* **1999**, *245*, 145. (c) Goller, A.; Grummt, U.-W. *Int. J. Quant. Chem.* **2000**, *77*, 727. (d) Nesterov, V. N.; Timofeeva, T. V.; Antipin, M. Y.; Clark, R. D. *Acta Crystallogr. C* **2000**, *C56*, 976. (e) Panja, S.; Bangal, P. R.; Chakravorti, S. *Chem. Phys. Lett.* **2000**, *329*, 377. (f) Bangal, P. R.; Panja, S.; Chakravorti, S. *J. Photoch. Photobio. A* **2001**, *139*, 5. (g) Panja, S.; Chakravorti, S. *Spectrochim. Acta A* **2002**, *58A*, 113.

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(7) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

(8) Unroe, M. R.; Reinhardt, B. A. *Synthesis* **1987**, 981.

(9) Our attempts to prepare cinnamaldehydes from *p*-iodoanisole and *o*-iodotoluene under Jeffery's conditions [2 equiv of acrolein, 0.03 equiv of Pd(OAc)$_2$, 1 equiv of ^{n}BuN$_4$Cl, and 2.5 equiv of NaHCO$_3$ in DMF at 20 °C] produced the desired products in 18 and 26% yields (96 h), respectively. *p*-Iodoanisole and *o*-iodotoluene were recovered in 79 and 54% yields, respectively.

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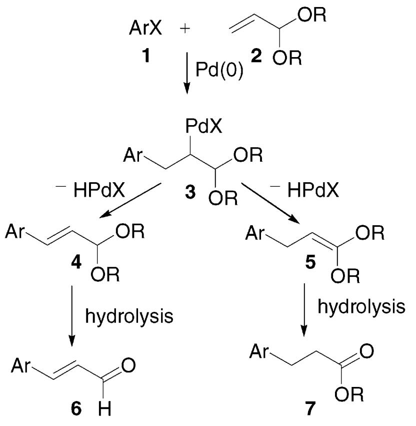
ization[10] and product yields are quite low. To avoid the polymerization problem, acrolein acetals have been used by Heck as three-carbon components.[10] However, this procedure is flawed by the formation of mixtures of the desired vinylic substitution products **4** and ester derivatives **7**,[11] due to the fact that the palladium hydride elimination from the carbopalladation intermediate **3** can involve both the available β hydrogens (Scheme 1). For example, the reaction of bromobenzene with acrolein dimethyl acetal gave the corresponding derivatives **4** and **7** in 56 and 39% yields, respectively.

Scheme 1



Some interesting results have been obtained by slightly modifying the original Heck conditions.[12] However, only two substituents have been explored (Me and ^{i}Pr) and, apparently, no mention has been made of propanoate ester byproducts. When we subjected *m*-bromotoluene to the modified Heck conditions, the reaction produced the corresponding cinnamaldehyde and propanoate ester in 62 and 35% yields, respectively.

Therefore, it appeared to be of interest to investigate further the palladium-catalyzed reaction of aryl halides with a three-carbon component so as to turn it into a general synthetically useful route to cinnamaldehydes. Particularly because of their higher thermal stability, we decided to explore the use of dialkyl acetals. Consequently, our task was to find conditions to control the direction of the key palladium hydride elimination.

p-Iodoanisole and acrolein diethyl acetal **2** (R = Et) were employed as the model system. Initial attempts were carried out using $Pd(OAc)_2$ as the precatalyst, Na_2CO_3 as the base (employment of nitrogen bases has been reported to afford a mixture of products),[10] $^nBu_4NCl$ as the added salt, and a variety of phosphine ligands at temperatures ranging from 60 to 90 °C in DMF. However, formation of mixtures of the aryl acetal **4a** and the ester **7a** (the major component) was still observed with PPh_3, $(o\text{-tol})_3P$, $(p\text{-MeO}-C_6H_4)_3P$, $[2,6\text{-(MeO)}_2-C_6H_3]_3P$, $[2,4,6\text{-(MeO)}_3-C_6H_2]_3P$, and $(p\text{-Cl}-C_6H_4)_3P$. Omitting phosphine ligands did not provide any beneficial effect, the ester **7a** still being the main reaction product (Table 1, entries 1 and 2). Only after switching to KOAc (and omitting phosphine ligands) did the mixture contain predominantly the desired **4a** (Table 1, entries 3 and 4). Of the possible (*E*)- and (*Z*)-isomers, only the (*E*)-isomer was present, as indicated by the large coupling constant (16 Hz) of the vinyl hydrogens. The yield increased to 78% in 2 h by adding 1.5 equiv of K_2CO_3[13] (Table 1, entry 7). But the best result in terms of reaction time, yield (including the isolated cinnamaldehyde derivative), and ratio of **4a** to **7a** was obtained by using 2 equiv of $^nBu_4NOAc$, 1.5 equiv of K_2CO_3, and 1 equiv of KCl (Table 1, entry 10).

Table 1. Bases and Salts in the Reaction of *p*-Iodoanisole and Acrolein Diethyl Acetal in the Presence of $Pd(OAc)_2$[a]

entry	base (equiv)	salt (1 equiv)	*T* (°C)	time (h)	% yield[b] **4a**[c]	% yield[b] **7a**
1	Na_2CO_3 (2.5)	$^nBu_4NCl$	60	18	28	47
2	Na_2CO_3 (2.5)	$^nBu_4NCl$	90	3.5	30	61
3	KOAc (2)	$^nBu_4NCl$	60	17	51 (2)	33
4	KOAc (2)	$^nBu_4NCl$	90	3	47	34
5	KOAc (2), $NaHCO_3$ (1.5)	$^nBu_4NCl$	60	18	56 (5)	29
6	KOAc (2), K_2CO_3 (1.5)	$^nBu_4NCl$	60	4	43 (4)	28
7	KOAc (2), K_2CO_3 (1.5)	$^nBu_4NCl$	90	2	78	21
8	KOAc (2), K_3PO_4 (1.5)	$^nBu_4NCl$	90	3.5	59 (6)	21
9	$^nBu_4NOAc$ (2), K_2CO_3 (1.5)	$^nBu_4NCl$	90	4	57 (4)	14
10	$^nBu_4NOAc$ (2), K_2CO_3 (1.5)	KCl	90	3	73 (8)	5

[a] Reactions were conducted on a 0.5 mmol scale in starting *p*-iodoanisole in DMF (2 mL) using 1 equiv of *p*-iodoanisole, 3 equiv of acrolein diethyl acetal, and 0.03 equiv of $Pd(OAc)_2$. [b] Yields are given for isolated products. [c] Figures in parentheses refer to isolated *p*-methoxycinnamaldehyde.

The cinnamaldehyde product could be obtained upon exposing **4a** to 2 N HCl at room temperature. However, the preparation of **6a** was conveniently carried out as a one-pot process, omitting the isolation of **4a** (2 N HCl was added to the crude reaction mixture). Compound **6a**, in this case, was isolated in 88% overall yield. Therefore, the one-pot protocol was employed when the reaction was extended to include other aryl iodides and bromides.

Under the best conditions developed so far [$Pd(OAc)_2$, $^nBu_4NOAc$, K_2CO_3, KCl, and DMF, at 90 °C until the disappearance of **1** followed by the addition of 2 N HCl to the crude reaction mixture],[14] the reaction proceeds very

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[10] Zebovitz, T. C.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3907.

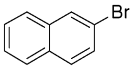
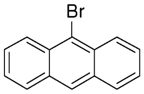
[11] Ketene acetals **5** have been reported to be unstable under vinylic substitution conditions and to form ester derivatives even under careful anhydrous conditions; see: ref 10.

[12] Lee, J. T.; Kim, J. I. *Daehan Hwahak Hwoejee* **1984**, *28*, 335. Conditions used: ArBr (1 equiv), acrolein diethyl acetal (1.2 equiv), $Pd(OAc)_2$ (0.01 equiv), $(o\text{-tol})_3P$ (0.02 equiv), and Et_3N (3 equiv) at 100 °C. Heck conditions:[10] ArBr (1 equiv), acrolein dimethyl acetal (1 equiv), $Pd(OAc)_2$ (0.008 equiv), $(o\text{-tol})_3P$ (0.064 equiv), and Et_3N (1 equiv) at 100 °C.

[13] Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Synlett* **1996**, 568.

[14] **Typical Procedure for the Preparation of Cinnamaldehydes.** To a stirred solution of *p*-iodoanisole (0.117 g, 0.5 mmol) in 2.0 mL of DMF were added acrolein diethyl acetal (0.229 mL, 1.5 mmol), $^nBu_4NOAc$ (0.302 g, 1.0 mmol), K_2CO_3 (0.104 g, 0.75 mmol), KCl (0.037 g, 0.5 mmol), and $Pd(OAc)_2$ (0.003 g, 0.015 mmol). The mixture was stirred for 1.5 h at 90 °C. After the mixture was cooled, 2 N HCl was slowly added and the reaction mixture was stirred at room temperature for 10 min. Then, the mixture was diluted with ether and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 90/10 v/v *n*-hexane/ethyl

Table 2. Palladium-Catalyzed Synthesis of Cinnamaldehydes **6** from Aryl Halides **1** and Acrolein Diethyl Acetal[a]

entry	aryl halide **1**	time (h)	yield %[b] of **6**	
1	p-MeO-C$_6$H$_4$-I	1.5	88	**a**
2	p-MeO-C$_6$H$_4$-Br	8	81	**a**
3	m-MeO-C$_6$H$_4$-I	3.5	85	**b**
4	o-MeO-C$_6$H$_4$-I	10	57	**c**
5	p-Me$_2$N-C$_6$H$_4$-Br	8	74	**d**
6	p-Me-C$_6$H$_4$-I	3	81	**e**
7	p-Me-C$_6$H$_4$-Br	4	74	**e**
8	m-Me-C$_6$H$_4$-I	3.5	91	**f**
9	m-Me-C$_6$H$_4$-Br	4	70	**f**
10	o-Me-C$_6$H$_4$-I	2.5	80	**g**
11	o-Me-C$_6$H$_4$-Br	7	61	**g**
12	p-Bu^t-C$_6$H$_4$-I	8.5	71	**h**
13	3,5-Me$_2$-C$_6$H$_3$-Br	9	65	**i**
14	PhBr	3	85	**j**
15	p-Ph-C$_6$H$_4$-Br	4	89	**k**
16		15	70	**l**
17		2	70	**m**
18	p-F-C$_6$H$_4$-I	5	83	**n**
19	p-F-C$_6$H$_4$-Br	5	83	**n**
20	m-F-C$_6$H$_4$-I	5	81	**o**
21	m-F-C$_6$H$_4$-Br	5	74	**o**
22	m-CF$_3$-C$_6$H$_4$-I	3.5	75	**p**
23	m-CF$_3$-C$_6$H$_4$-Br	2	80	**p**
24	o-F-C$_6$H$_4$-I	5.5	70	**q**
25	p-NC-C$_6$H$_4$-Br	25	52	**r**
26	p-EtOOC-C$_6$H$_4$-I	1.5	79	**s**
27	p-MeCO-C$_6$H$_4$-I	0.5	70	**t**
28	p-Cl-C$_6$H$_4$-I	3.5	83	**u**
29	p-OHC-C$_6$H$_4$-Br	1.5	75	**v**
30	m-OHC-C$_6$H$_4$-Br	1.5	75	**w**
31	o-OHC-C$_6$H$_4$-Br	3	70	**x**
32	p-O$_2$N-C$_6$H$_4$-I	5	60	**y**
33	p-O$_2$N-C$_6$H$_4$-Br	5	70	**y**
34	m-O$_2$N-C$_6$H$_4$-Br	5	64	**z**

[a] Reactions were conducted on a 0.5 mmol scale in starting aryl halides in DMF (2 mL) at 90 °C using 1 equiv of aryl halide, 3 equiv of acrolein diethyl acetal, 0.03 equiv of Pd(OAc)$_2$, 2 equiv of ^{n}Bu$_4$NOAc, 1.5 equiv of K$_2$CO$_3$, and 1 equiv of KCl. [b] Yields are given for isolated products.

smoothly with high regioselectivity. The elimination of HPdXL$_n$ species from **3** occurs so as to favor the formation of the aryl acetal **4**. Propanoate esters have been obtained in yields ranging from traces to 10%.

As shown in Table 2, a variety of functional groups are tolerated in the aryl halides, including ether, aldehyde, ketone, ester, dialkylamino, nitrile, and nitro groups. Cinnamaldehydes were isolated in good to high yields, with many neutral, electron-rich, and electron-poor aryl iodides and bromides. No significant influence of the substituents in the aryl halides on the ratio of **6** to **7** was observed. Both electron-poor and electron-rich aryl halides yielded cinnamaldehydes as the main products. On the contrary, under typical Heck conditions, the reaction appears to be influenced by the nature of the aryl halide. For example, the reaction of p-bromonitrobenzene with acrolein dimethyl acetal gave exclusively (59% yield) the corresponding propanoate ester, as it might be expected on the basis of a presumed weaker hydridic character of the benzylic hydrogen in the corresponding carbopalladation adduct **4**.[10] Under our conditions, p-bromonitrobenzene gives the cinnamaldehyde product in 70% yield (Table 2, entry 33).

Remarkably, our process can be successfully applied to the preparation of cinnamaldehydes bearing *para* dialkylamino substituents (Table 2, entry 5), an important class of compounds[5,6] that cannot be prepared by using the Heck conditions (dark tar-like nonvolatile products were obtained)[10] or the vinylogation of p-dialkylaminobenzaldehydes (they have been reported not to react at all).[15] The presence of substituents close to the oxidative addition site does not hamper the reaction (Table 2, entries 4, 10, 11, 17, 24, 31).

In conclusion, we have shown that an appropriate selection of bases and added salts can provide an efficient and straightforward route for the palladium-catalyzed synthesis

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acetate) to give 0.071 g (88% yield) of p-methoxycinnamaldehyde **6a**: mp 56−7 °C.; lit. mp 57−58.5 °C (Gulyi, S. E. *Zhurnal Organicheskoi Khimii* **1983**, *19*, 808); IR (KBr) 1667, 1250, 1018, 977 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.62 (d, J_1 = 7.8 Hz, 1H), 7.55−7.49 (m, 2H), 7.43 (d, J = 15.8 Hz, 1H), 6.98−6.93 (m, 2H), 6.61 (dd, J_1 = 15.8 Hz, J_2 = 7.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 194.0, 162.6, 153.1, 130.7, 127.1, 126.8, 114.9, 55.8. Anal. Calcd for C$_{10}$H$_{10}$O$_2$: C, 74.06; H, 6.21. Found C, 74.11; H, 6.24.

(15) Daubrasse, N.; Francesch, C.; Rolando, C. *Tetrahedron* **1998**, *54*, 10761.

of cinnamaldehydes from acrolein diethyl acetal and a variety of aryl iodides or bromides. The process is quite general and tolerates many important functional groups.

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Supporting Information Available: Typical experimental procedure for the preparation of cinnamaldeydes and characterization data for all the compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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