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Preliminary communication

THE PALLADIUM-CATALYZED CONJUGATE ADDITION TYPE REACTION OF ARYL IODIDES WITH α,β-UNSATURATED ALDEHYDES

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Summary

α,β-Enals have been shown to react with aryl iodides in the presence of a palladium catalyst with selective formation of conjugate addition type products.

During our studies on palladium-catalyzed reactions [1], we found that aryl iodides and α,β-enones react in the presence of catalytic amounts of palladium and triethylammonium formate with selective formation of conjugate addition type products [2]; as various common functional groups can be tolerated in the aryl unit, this procedure appears to provide new synthetic possibilities. It thus seemed to us of interest to evaluate the effectiveness of this reaction with α,β-enals for, while the conjugate addition of a variety of organometallic reagents [1—3] to α,β-enones has been investigated in detail, the conjugate addition to α,β-enals has been largely neglected. The relatively few data available on this matter, inadequate for clear generalizations, indicate that α,β-enals react with carbon nucleophiles (organocuprates) as 1,4- as well as 1,2-acceptors [4] which makes them unattractive substrates for Michael reactions.

We describe here the results obtained in an extension of our palladium-catalyzed reaction to α,β-enals. Cinnamaldehyde was used as the α,β-enal, and was treated with aryl iodides (I) in the presence of catalytic amounts of palladium to give 3-phenyl-3-arylpropanals (II) (3,3-diarylpropanals may be useful intermediates for the synthesis of various derivatives reported to show pharmacological activity [5]) according to equation 1.

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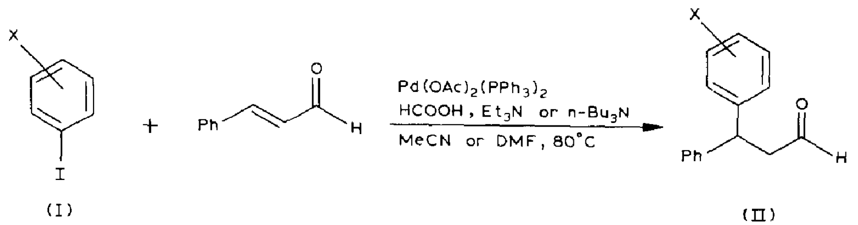


(1)

TABLE 1

PALLADIUM-CATALYZED CONJUGATE ADDITION TYPE REACTIONS OF ARYL IODIDES WITH CINNAMALDEHYDE

Entry	Aryl iodide (I), X =	Reaction time (h)	Yield of II[a,b]	M.p. °C (lit.m.p.)	^{1}H NMR δ ($CDCl_3$) (ppm)
a[c,d]	H	5	35 (6, —)	168—170[e] (176—177) [5a]	9.75 (m, 1H); 7.68—7.08 (m, 10H); 4.62 (t, *J* 7.5 Hz, 1H); 3.12 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H)
b[c,f]	*p*-Me	3.5	21 (4, 22)	140—141[e]	9.77 (m, 1H); 7.39—7.03 (m, 9H); 4.57 (t, *J* 7.5 Hz, 1H); 3,11 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 2.25 (s, 3H)
c[c,d]	*m*-$HOCH_2$	5.5	40 (4, 26)	38—41	9.76 (m, 1H); 7.65—7.03 (m, 9H); 4.76—4.48 (m, 3H); 3.12 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 2.26 (bs, 1H, exchange with D_2O)
d[c,f]	*o*-MeO	7	50	138—140[e]	9.75 (m, 1H); 7.69—6.85 (m, 9H), 5.05 (t, *J* 7.5 Hz, 1H); 3.79 (s, 3H); 3.09 (dd, *J* 2.2 Hz, *J* 7.5 Hz, 2H)
e[c,f]	*p*-MeO	3.5	72 (4, 15)	123—124[e]	9.75 (m 1H); 7.53—6.73 (m, 9H); 4.57 (t, *J* 7.5 Hz, 1H); 3.72 (s, 3H); 3.07 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H)
f[c,f]	*m*-MeCONH	7	22 (—, 67)	85—89	9.92 (bs, 1H, exchange with DCl); 9.72 (m, 1H); 7.62—6.95 (m 9H); 4.60 (t, *J* 7.5 Hz, 1H); 3.17 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 1.99 (s, 3H)[g]
g[c,f]	*p*-MeCONH	3	66 (7, 18)	105—106	9.92 (bs, 1H, exchange with DCl); 9.73 (m, 1H); 7.72—7.14 (m, 9H); 4.59 (t, *J* 7.5 Hz, 1H); 3.20 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 2.02 (s, 3H)[g]
h[c,f]	*p*-HO	4	50 (35, —)[h,i]	85—88	9.75 (m, 1H); 7.38—6.95 (m, 9H); 4.62 (t, *J* 7.5 Hz, 1H); 3.10 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 2.2 (s, 3H)
i[l,d]	*p*-HO, *m*-EtOCO	7	45 (—, 9)	165—168[e]	10.80 (bs, 1H, exchange with D_2O); 9.82 (m, 1H); 7.78 (d, *J* 3.0 Hz, 1H); 7.56—7.18 (m, 6H); 6.93 (d, *J* 9.0 Hz, 1H); 4.57 (t, *J* 7.5 Hz, 1H); 4.42 (q, *J* 6.3 Hz, 2H); 3.14 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H); 1.39 (t, *J* 6.3 Hz, 3H)

[a] Reaction conditions were not optimized. Yields are based on the cinnamaldehyde taken and refer to isolated products. Satisfactory microanalyses and mass spectra were obtained for all the isolated products. [b] Figures in parentheses refer to isolated vinylic substitution products and starting cinnamaldehyde, respectively. [c] MeCN. [d] Bu_3N. [e] As the 2,4-dinitrophenylhydrazone. [f] Et_3N. [g] DMSO-d_6. [h] GLC yields.
[i] Isolated (and characterized) as the corresponding acetyl derivatives in 36 and 27% yield, respectively.
[l] DMF.

The reactions were carried out as follows. Cinnamaldehyde (3.4 mmol) was allowed to react for an appropriate period in acetonitrile or dimethylformamide (1 ml) with an excess of the aryl iodide (8.16 mmol), triethylamine or tri-n-butylamine (11.56 mmol), and formic acid (8.98 mmol) in the presence of bis-(triphenylphosphine)palladium diacetate (0.017 mmol) at 80°C under argon. The mixture was then diluted with diethyl ether, washed with water (2 *N* HCl, saturated $NaHCO_3$ and water when tri-n-butylamine was used), and the ethereal layer was dried ($MgSO_4$) then concentrated under reduced pressure. Pure products were obtained by preparative HPLC or flash chromatography, using petroleum ether/ethyl acetate mixtures as eluants.

As observed in the reactions of α,β-enones [2], the product mixtures contain small amounts of materials derived from palladium-catalyzed vinylic substitution. All but one of the examples we have studied, however, gave very good conjugate addition/vinylic substitution (CA/VS) ratios. Only in the case of 4-hydroxyphenyl iodide (see Table 1, entry h) were substantial amounts of the vinylic substitution products observed (CA/VS = 1.4), paralleling the result of the analogous reaction with benzalacetone (CA/VS = 2.3). Whatever the origin of this effect of the presence of the free hydroxy group on the CA/VS ratio, it is noteworthy that replacement of the phenolic hydrogen by a methyl group raised the ratio to about 10 (as determined by NMR analysis of the worked up reaction mixture; analogous behaviour was observed with benzalacetone).

Products derived from palladium-catalyzed coupling and reduction of aryl iodides were also obtained.

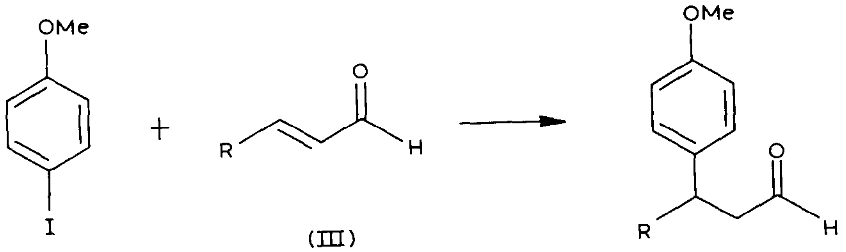
The efficiency of this new route to conjugate addition type products of α,β-enals was also tested by treating some commercially available α,β-enals with 4-methoxyphenyl iodide (eq. 2). The results are summarized in Table 2.

TABLE 2

PALLADIUM-CATALYZED CONJUGATE ADDITION TYPE REACTIONS OF 4-METHOXYPHENYLIODIDE WITH α,β-ENALS

Entry	Starting material (III) R =	Reaction time (h)	Yield of IV^{a,b}	M.p. (°C)	^{1}H NMR δ ($CDCl_3$) (ppm)
a^{c,d}	o-O_2N-C_6H_4-	7	60 (3, 10)	86—87	9.79 (m, 1H); 7.97—6.80 (m, 8H); 5.30 (t, *J* 7.5 Hz, 1H); 3.75 (s, 3H); 3.17 (dd, *J* 1.8 Hz, *J* 7.5 Hz, 2H)
b^{c,e}	p-Me_2N-C_6H_4-	5	44 (14, 14)	58—62^f	9.77 (m, 1H); 7.33—6.63 (m, 8H); 4.49 (t, *J* 7.5 Hz, 1H); 3,75 (s, 3H); 3.08 (m, 2H); 2.87 (s, 6H)
c^{c,e}	$Me(CH_2)_2$-	2	36	83—85^f	9.70 (m, 1H); 7.00 (AA'BB' system, *J* 9.0 Hz, 4H); 3.77 (s, 3H); 3.15 (m, 1H); 2.65 (dd, *J* 2.1 Hz, *J* 7.5 Hz, 2H); 1.76—0.65 (m, 7H)

[a] Reaction conditions were not optimized. Yields are based on α,β-enal taken and refer to isolated products. Satisfactory microanalyses and mass spectra were obtained for all the isolated products. [b] Figures in parentheses refer to isolated vinylic substitution products and starting materials, respectively. [c] MeCN. [d] Et_3N. [e] Bu_3N. [f] As the 2,4-dinitrophenylhydrazone.



(III)

(IV)

(2)

Under the conditions used, yields are generally only moderate to good. However, there may be scope for optimization. In any case, even with the results obtained, the reaction may represent the method of choice for preparation of saturated aldehydes containing a functionalyzed β-aryl group.

The scope and the applications of this palladium-catalyzed reaction on α,β-enals, like those on α,β-enones [2], are currently under investigation.

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