

Preliminary communication

THE REACTION OF ARYL IODIDES WITH HINDERED $\alpha,\beta,\gamma,\delta$ -DIENONES IN THE PRESENCE OF THE $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ -TRIALKYLAMMONIUM FORMATE REAGENT

A. ARCADI, F. MARINELLI,

Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università degli Studi, Via Assergi 4, 67100 L'Aquila (Italy)

and S. CACCHI*

Istituto di Chimica Organica, Via del Castro Laurenziano 9, 00161 Roma (Italy)

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Summary

Hindered $\alpha,\beta,\gamma,\delta$ -dienones have been shown to react with aryl iodides in the presence of the $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ -trialkylammonium formate reagent to give mainly 1,4-conjugate addition type products. The $\alpha,\beta,\gamma,\delta$ -dienones were prepared through reaction of the corresponding vinyl triflates with α,β -enones in the presence of $\text{Pd}(\text{OAc})_2$, K_2CO_3 , and tetrabutylammonium chloride at room temperature.

The palladium-catalyzed reductive addition of aryl iodides to carbon-carbon multiple bonds provides a versatile method for the synthesis of conjugate addition type products from α,β -enones [1a,b] and α,β -enals [1b,2], of arylated olefins from alkynes [3], and of arylated allylic alcohols from propargyl alcohols [4]. As part of a program devoted to the investigation of this procedure in organic synthesis we have examined the reactions of aryl iodides with hindered $\alpha,\beta,\gamma,\delta$ -dienones in the presence of a palladium-trialkylammonium reagent, and the results are presented here. The reactions were carried out on the commercially available β -ionone (**1a**) and on various $\alpha,\beta,\gamma,\delta$ -dienones (**1b–1e**), by treating them with aryl iodides (**2**) in the presence of $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$, tri-*n*-butylamine and formic acid (Scheme 1).

The starting $\alpha,\beta,\gamma,\delta$ -dienones (**1b–1e**) were prepared in good to high yield by treating the corresponding vinyl triflates (**6**) and α,β -enones (**7**) in the presence of $\text{Pd}(\text{OAc})_2$, potassium carbonate, and tetrabutylammonium chloride, the catalyst system used by Jeffery [5] for the reaction of vinyl iodides with olefins (Table 1).

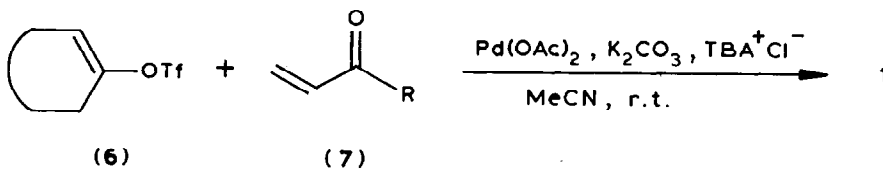
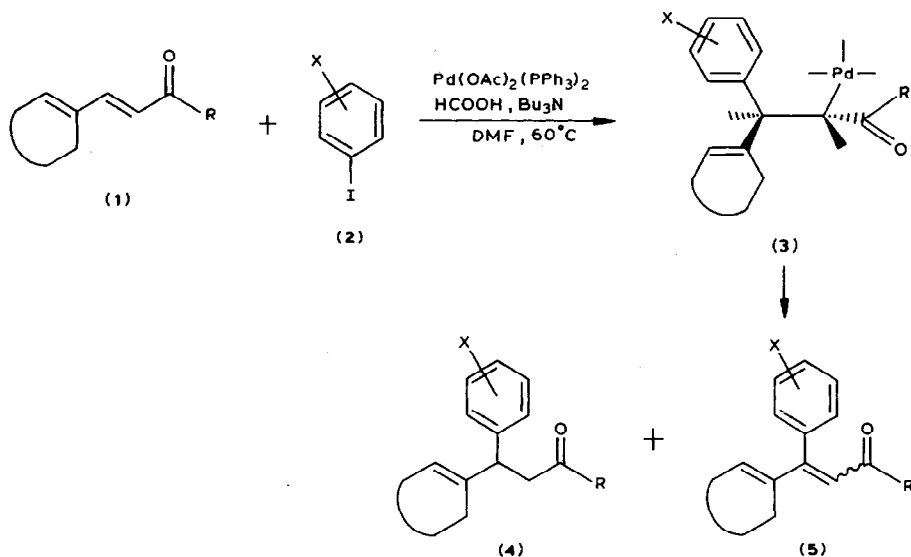


TABLE I. IR AND ^1H NMR SPECTRAL DATA OF $\alpha,\beta,\gamma,\delta$ -DIENONES (I) PREPARED ^{a,b}

$\alpha,\beta,\gamma,\delta$ -Dienone	R	Yield (%) ^c	M.p. (°C)	IR $\nu(\text{cm}^{-1})$ ^d	^1H NMR $\delta(\text{CDCl}_3)$ (ppm) ^e
	Et	77	103–104	1730, 1690, 1665, 1605 ^f	7.23 (d, <i>J</i> 17.0 Hz, 1H), 6.33 (d, <i>J</i> 17.0 Hz, 1H), 6.19 (m, 1H), 4.71 (m, 1H), 2.58 (q, <i>J</i> 7.5 Hz, 2H), 2.00 (s, 3H), 1.10 (t, <i>J</i> 7.5 Hz, 3H), 0.88 (s, 3H), 0.84 (s, 3H)
	Et	67	oil	1690, 1665, 1620, 1600, 985, 975 ^g	7.28 (d, <i>J</i> 16.5 Hz, 1H), 6.12 (d, <i>J</i> 16.5 Hz, 1H), 5.93 (s, 1H), 2.59 (q, <i>J</i> 7.5 Hz, 2H), 1.91 (s, 2H), 1.39 (s, 2H), 1.12 (t, <i>J</i> 7.5 Hz, 3H), 1.08 (s, 6H), 0.97 (s, 6H)
	Et	80	oil	1690, 1655, 1615, 1590, 975 ^g	7.74 (d, <i>J</i> 15.7 Hz, 1H), 6.18 (d, <i>J</i> 15.7 Hz, 1H), 2.59 (q, <i>J</i> 7.5 Hz, 2H), 2.77–2.4 (m, 1H), 2.27–2.0 (m, 2H), 1.87 (s, 3H), 1.77–1.43 (m, 4H), 1.1 (t, <i>J</i> 7.5 Hz, 3H), 1.07 (s, 3H), 1.0 (s, 3H)
	Me	81	oil	1690, 1665, 1615, 1580, 975 ^g	7.70 (d, <i>J</i> 16.5 Hz, 1H), 6.18 (d, <i>J</i> 16.5 Hz, 1H), 2.79–2.46 (m, 1H), 2.29 (s, 3H), 2.32–2.06 (m, 2H), 1.90 (s, 3H), 1.79–1.49 (m, 4H), 1.05 (d, <i>J</i> 7.0 Hz, 3H)

^a The starting vinyl triflates were prepared as described in ref. 6. ^b Satisfactory microanalyses were obtained. ^c Yields refer to single, not optimized runs, are based on the amount of vinyl triflate initially used, and refer to isolated products. Disappearance of the starting material was monitored by TLC or GLC. ^d IR spectra were recorded with a Perkin-Elmer 683 spectrometer. ^e ^1H NMR spectra were recorded with a Varian EM390 spectrometer. ^f KBr. ^g Liquid film.



SCHEME I


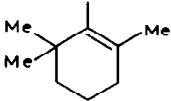
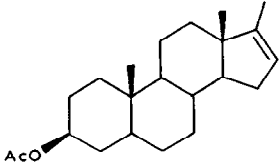
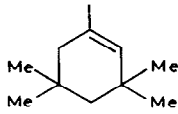
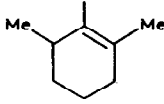
This procedure appears to give comparable or better results than those previously reported [6], and employs milder conditions. In a typical example of the reaction of a vinyl triflate (6) with an α,β -enone (7), 3β -acetoxy- 5α -androst-16-en-17-yl triflate (0.300 g, 0.65 mmol) was added to pent-1-en-3-one (0.164 g, 1.95 mmol), tetrabutylammonium chloride (0.181 g, 0.65 mmol), potassium carbonate (0.224 g, 1.62 mmol), and palladium diacetate (4.3 mg, 0.019 mmol) in DMF (2 ml). The mixture was stirred at room temperature under argon for 1.5 h, then, water and diethyl ether were added, and the organic layer was separated, dried (MgSO_4) and evaporated under reduced pressure to leave a residue which was subjected to flash chromatography with 9/1 n-hexane/AcOEt as eluant to give **1b** (0.200 g, 77% yield).

In a typical example of the reaction of a $\alpha,\beta,\gamma,\delta$ -dienone (1) with an aryl iodide (2), the starting β -ionone (**1a**; 0.300 g, 1.56 mmol) was treated in dimethylformamide (1 ml) with an excess of 4-hydroxyphenyl iodide (0.823 g, 3.74 mmol), tri-*n*-butylamine (0.982 g, 5.30 mmol), and 99% formic acid (0.155 ml, 4.12 mmol) in the presence of bis(triphenylphosphine)palladium diacetate (23 mg, 0.0031 mmol) at 60°C under argon. After 20 h the mixture was diluted with diethyl ether then washed with 2*N* HCl, saturated NaHCO_3 and water. The ethereal layer was separated, dried (MgSO_4), and evaporated under reduced pressure to leave a residue, which was subjected to preparative HPLC* (LiChrorep 15- 25μ , Merck), with 88/12 n-hexane/AcOEt as eluant to give unchanged β -ionone (24 mg, 8% yield), **4b** (0.278 g, 62% yield), and **5b** (0.116 g, 26% yield).

As expected from consideration of steric effects, only products with the new carbon-carbon bond on the β -carbon were isolated in significant yield (Table 2). Furthermore, the reactions usually gave the conjugate addition type derivatives **4** as

* Preparative HPLC was performed with a Chromatospac Prep 10 (Jobin Yvon) equipped with a PrepLC/System 500A solvent delivery system and refractive index detector (Waters).

TABLE 2
 PALLADIUM-CATALYZED REACTION OF ARYL IODIDES (2) WITH $\alpha,\beta,\gamma,\delta$ -DIENONES (1)

Entry	Compound 1	Compound 2 X	Reaction time (h)	Yield of 4 (%) ^{a,b}	
		R			
a)		Me	4-MeO	24	61 (29, 5)
b)		Me	4-HO	20	62 (8, 26)
c)		Me	4-Me	30	34 (54, -)
d)		Me	3-MeCONH	48	28 (70, -)
e)		Me	2-MeO	48	16 (77, -)
f)		Et	4-HO	72	41 (13, -)
g)		Et	4-MeO	30	53 (27, -)
h)		Et	4-HO	30	50 (7, 25)
i)		Et	4-MeO	40	8 (45, 22) ^c
l)		Et	4-HO	30	- (5, 63)
m)		Me	4-MeO	24	39 (23, 17) ^c

^a Unless otherwise stated, yields are given for isolated products, refer to single, not optimized runs, and are based on the starting $\alpha,\beta,\gamma,\delta$ -dienone. ^b Figures in parentheses refer to the isolated starting material and vinylic substitution product, respectively. ^c Determined by ¹H NMR analysis of the worked-up reaction mixture.

the main products. The vinylic substitution derivatives **5** were isolated as the main products only from the reaction of compound **1d** with 4-methoxy- or 4-hydroxyphenyl iodide * (Table 2, entries i and l). The presence of the 4-hydroxy group has

* Compounds **5i** and **5l** were isolated as an ca. 60/40 mixture of isomeric olefins (as determined by ¹H NMR spectroscopy), the *E/Z* configurations of which were not assigned.

been observed previously to lead to lower conjugate addition (CA)/vinylic substitution (VS) ratios than are observed in the presence of other functional groups whereas the 4-methoxy group gives good CA/Vs ratios (for example, with benzalacetone and cinnamaldehyde the CA/Vs ratios were about 10) [2]; these results (Table 2, entries i and l) might be accounted for in terms of steric factors affecting

TABLE 3
CHARACTERIZATION OF COMPOUNDS 4a-4h^a

Compound	M.p. (°C)	IR $\nu(\text{cm}^{-1})$ ^b	¹ H-NMR $\delta(\text{CDCl}_3)$ (ppm) ^c
4a	82-83	1710, 1605, 1250, 1040, 820 ^d	6.92 (AA'BB' system, 4H), 4.33 (dd, <i>J</i> 2.5, 8.5 Hz, 1H), 3.76 (s, 3H), 3.32 (dd, <i>J</i> 8.5, 18.7 Hz, 1H), 2.78 (dd, <i>J</i> 2.5, 18.7 Hz, 1H), 2.20 (s, 3H), 2.07-1.83 (m, 2H), 1.78-1.40 (m, 4H), 1.28 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H)
4b	128-129	3395, 1695, 1610, 830 ^d	6.85 (AA'BB' system, 4H), 6.32 (s, exchange with D ₂ O, 1H), 4.31 (dd, <i>J</i> 2.5, 8.5 Hz, 1H), 3.33 (dd, <i>J</i> 8.5, 18.7 Hz, 1H), 2.79 (dd, <i>J</i> 2.5, 18.7 Hz, 1H), 2.22 (s, 3H), 2.07-1.83 (m, 2H), 1.80-1.40 (m, 4H), 1.27 (s, 3H), 1.03 (s, 3H), 1.00 (d, 3H)
4c	89-92	1710-810 ^d	7.04 (m, 4H), 4.37 (dd, <i>J</i> 2.5, 8.5 Hz, 1H), 3.32 (dd, <i>J</i> 8.5, 18.7 Hz, 1H), 2.78 (dd, <i>J</i> 2.5, 18.7 Hz, 1H), 2.28 (s, 3H), 2.21 (s, 3H), 2.07-1.83 (m, 2H), 1.80-1.37 (m, 4H), 1.28 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H)
4d	150-151	3245, 1710, 1665, 1610, 795, 690 ^d	9.85 (bs, 1H), 7.57-6.67 (m, 4H), 4.22 (bd, 1H), 3.44 (dd, <i>J</i> 8.5, 18.7 Hz, 1H), 2.67 (dd, <i>J</i> 2.0, 18.7 Hz, 1H), 2.26 (s, 3H), 2.02 (s, 3H), 2.07-1.77 (m, 2H), 1.71-1.37 (m, 4H), 1.20 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H) ^f
4e	67-69	1715, 1600, 1240, 1035, 750 ^d	7.35-7.10 (m, 2H), 7.00-6.74 (m, 2H), 4.47 (bt, 1H), 3.42 (s, 3H), 3.2-2.57 (m, 2H), 2.13 (s, 3H), 2.2-1.93 (m, 2H), 1.77-1.33 (m, 4H), 1.55 (s, 3H), 1.15 (s, 3H), 0.77 (s, 3H)
4f	91-94	3400, 1730, 1710, 1610, 1595, 830 ^d	6.92 (AA'BB' system, 4H), 6.43 (bs, exchange with D ₂ O, 1H), 5.48 (m, 1H), 4.69 (m, 1H), 3.86 (m, 1H), 2.93-2.70 (m, 2H), 2.00 (s, 3H), 0.92 (t, <i>J</i> 7.5 Hz, 3H), 0.78 (s, 6H)
4g	oil	1715, 1610, 1585, 1250, 1040, 830 ^e	6.95 (AA'BB' system, 4H), 5.28 (s, 1H), 3.76 (s, 3H), 3.69 (bt, 1H), 2.78 (m, 2H), 2.31 (m, 2H), 1.49 (s, 2H), 1.23 (s, 2H), 1.13-0.67 (m, 15H)
4h	oil	3380, 1700, 1610, 1590, 830 ^e	6.91 (AA'BB' system, 4H), 6.61 (s, exchange with D ₂ O, 1H), 5.30 (s, 1H), 3.69 (bt, 1H), 2.82 (m, 2H), 2.34 (m, 2H), 1.34 (s, 2H), 1.25 (s, 2H), 1.15-0.68 (m, 15H)

^a Satisfactory microanalyses were obtained. ^b IR spectra were recorded with a Perkin-Elmer 683 spectrometer. ^c ¹H-NMR spectra were recorded with a Varian EM390 spectrometer. ^d KBr. ^e Liquid film. ^f DMSO-*d*₆.

the reactivity of the addition intermediates **3**, but further systematic studies would be necessary to obtain conclusive information on this point.

Physical data for compounds **4** are listed in Table 3.

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