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Stereospecific Preparation of Ethyl *(E)* and *(Z)*-3-Aryl-3-phenylpropenoates by Heck Reaction.

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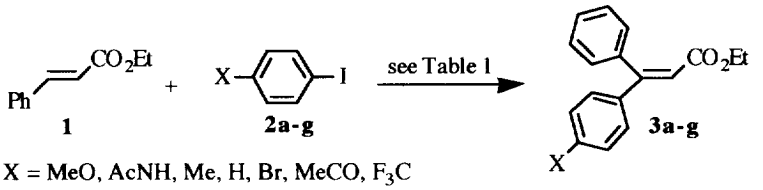
Abstract: Ethyl cinnamate reacts with several *para*-substituted aryl iodides under Jeffery-Larock conditions ($Pd(OAc)_2$, $NaHCO_3$, *n*-Bu_4NBr, DMF, Δ) to give ethyl *(E)*-3-aryl-3-phenylpropenoates as major compounds. The reaction of *para*-substituted ethyl cinnamates with iodobenzene under analogous conditions affords the corresponding *Z* isomers. The initially stereodefined alkene formed under Heck conditions undergoes a slow isomerization. Copyright © 1996 Published by Elsevier Science Ltd

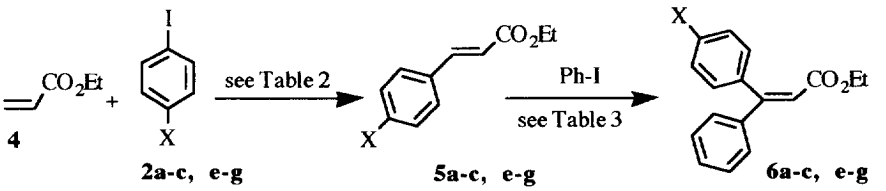
The palladium-catalyzed arylation and vinylation of alkenes (Heck reaction)[1] has aroused an increasing interest in the last few years and a large number of publications has appeared concerning synthetic applications, improvements of traditional Heck conditions, the use of triflates and arenediazonium salts as reagents, studies of regio- and stereoselectivity and new discoveries on mechanistic features.[2] In most of these papers the substitution pattern of the olefin is quite simple (monosubstituted or 1,1-disubstituted), less being known about arylation and alkenylation of 1,2-disubstituted or trisubstituted alkenes.[1a]

As the mechanism of the reaction includes *syn* addition of organopalladium intermediate to the olefin and *syn* elimination of palladium hydride, the sequential treatment of ethyl acrylate with two different aryl halides would allow the stereospecific preparation of either (*Z*) or (*E*)-β,β-diarylacrylates depending on which aryl derivative is introduced first. Some β,β-diarylacrylates are useful intermediates in the synthesis of angiotensin II antagonists,[3] platelet activating factor (PAF) antagonists,[4] and SRS-A (slow-reacting substance of anaphylaxis) antagonists.[5] They are usually prepared by Wadsworth-Emmons reaction[3,4a] leading to 1:1 mixtures of *cis* and *trans* isomers. Aldol condensation related methodologies[4a] give also mixtures of isomers. To our knowledge few exemples have been described on the arylation and alkenylation of β-substituted-α,β-unsaturated carbonyl compounds. In 1979 Heck reported[1a] the reaction of methyl acrylate with two equivalents of bromobenzene in one operational step to give methyl 3,3-diphenylacrylate. The ethyl ester was also obtained in small amounts in the reaction of iodobenzene with ethyl acrylate at room temperature under high pressure conditions.[6] The combined use of high temperature and high pressure increases considerably the yield of β,β-disubstituted product. One case of β,β-diarylpropenamide of undetermined stereochemistry has been found in a recent work on the Heck reaction with aryl iodides bound to a solid support.[7] Mixtures of *cis/trans* isomers, together with variable amounts of hydroarylation products and biphenyls have been isolated in the Pd(0)-catalyzed reaction of arylazo aryl sulfones with ethyl cinnamate.[8] In a Japanese patent[4a] the Heck reaction has also been claimed as an alternative method to Wadsworth-Emmons reaction for the preparation of diarylacrylates, but the stereochemical outcome of the reaction is not clarified. Very recently Cacchi *et al* have published[9] the vinylation of β-substituted-α,β-unsaturated ketones and esters using triflate derivatives. Some precedents existed in the literature about intramolecular[10] and intermolecular[11] related reactions.

The work by Cacchi *et al* prompt us to present here our results on the stereospecific preparation of ethyl *(E)* and *(Z)*-3-aryl-3-phenylpropenoates by Heck reaction. They are collected in the Scheme and Tables 1-3.



X = MeO, AcNH, Me, H, Br, MeCO, F_3C



X = MeO, AcNH, Me, Br, MeCO, F_3C

Scheme

Table 1.- Heck reaction between ethyl cinnamate, **1**, and *para*-substituted aryl iodides, **2a-g**.

Run	2, X	[1] (M)	1/2/Pd(OAc)2/P(*o*-tol)3/ NaHCO3/*n*-Bu4NBr	Solvent/T (C)/ t (days)	% yield[a]	3/6[b]	mp (C) of 3
1	**2a**, MeO	0.19	1/2/0.1/0.2/2.5/1.1	DMF/120/3	78	75/25	39-41[c]
2	**2a**, MeO	0.38	1/2/0.1/---/2.5/1.1	DMF/120/2	81	64/33	39-41[c]
3	**2a**, MeO	0.19	1/2/0.1/---/2.5/1.1	DMF/60/8	73 (85)	83/17	39-41[c]
4	**2b**, AcNH	0.38	1/1/0.1[d]/---/2.5/1.1	DMF/60/5	80	86/14	123-125[e]
5	**2c**, Me	0.19	1/2/0.1/0.2/2.5/1.1	DMF/120-130/5	89	80/20	oil[c]
6	**2c**, Me	0.38	1/2/0.1/---/1.1/2.5	DMF/80/2	67 (75)	100/0	oil[c]
7	**2d**, H	0.94	1/2/0.1/0.2/2.5/1.1	MeCN/80→120/7	50 (95)	------	oil[f]
8	**2d**, H	0.38	1/1g/0.1[d]/---/1.1/2.5	DMF/80/5	49 (77)	------	oil[f]
9	**2e**, Br	0.38	1/2/0.1[h]/---/2.5/1.1	DMF/80/2, then DMF/60/2	32 (43)	70/30	oil
10	**2f**, MeCO	0.57	1/2/0.1[h]/---/2.5/1.1	DMF/60/14	33 (49)[i]	75/25	oil[j]
11	**2f**, MeCO	0.57	1/2/0.1/---/1.1/2.5	DMF/100/9	44 (66)[k]	62/38	oil[j]
12	**2g**, F_3C	0.57	1/2/0.1[l]/---/2.5/1.1	DMF/60/9	19 (26)[m]	100/0	oil
13	**2g**, F_3C	0.57	1/2/0.1/---/2.5/1.1	DMF/100/8	61 (89)[n]	67/33	oil

[a] Overall isolated yields. In brackets the yields with respect to non recovered ethyl cinnamate, **1**. [b] Ratio of isomers calculated by ^{1}H-NMR integration. They were separated by column chromatography. All compounds showed spectroscopic behaviour as expected and correct elemental analysis when required. [c] Described as an oil in the lit.[8] Spectral data are coincident. [d] After three days of reaction more $Pd(OAc)_2$ was added (0.1 eq). [e] Lit.[12] mp 141-143C for a compound of undetermined stereochemistry. [f] Lit[13] bp 180-181C/760 mm Hg. [g] As **2d** was consumed faster than **1**, one more equivalent of **2d** was added after two days, and 0.5 equivalents after three days of reaction. [h] After two days of reaction more $Pd(OAc)_2$ was added (0.1 eq). [i] 4,4'-Diacetylbiphenyl (19% yield based on **2f**) was also isolated. [j] Pure samples of isomer **3f** could not be obtained. [k] 4,4'-Diacetylbiphenyl (14% yield based on **2f**) was also isolated. [l] After two days and after four days of reaction more $Pd(OAc)_2$ was added (0.1 eq in each case). [m] 4,4'-Bis(trifluoromethyl)biphenyl (6% yield based on **2g**) was also isolated. [n] Some 4,4'-Bis(trifluoromethyl)biphenyl mixed with **2g** was also obtained.

The reaction of ethyl cinnamate, **1**, with several *para*-substituted aryl iodides **2a-g**, give the *trans* isomers **3a-g** as major products as expected (Table1). After some experimentation Jeffery-Larock conditions[14] were adopted ($Pd(OAc)_2$, $NaHCO_3$, *n*-Bu_4NBr, DMF). Dimethylformamide was better than acetonitrile as solvent. Addition of phosphine ligands was not necessary. Excess of aryl iodide was generally used. At higher temperature (100-130°C *versus* 60-80°C) the reaction is accelerated but the stereospecificity decreases (in Table 1 compare runs 1, 2 and 3; runs 5 and 6; runs 10 and 11; runs 12 and 13). It occurs an isomerization of the initially stereodefined alkene favoured by electron-donating substituents. With electron-withdrawing substituents (MeCO, F_3C) in the *para* position of the aryl iodide a side reaction arises, i.e. the reductive coupling to give the corresponding biphenyls (runs 10-13 in Table 1).

Ethyl 3-arylpropenoates, **5a-c, e-g**, were prepared from ethyl acrylate, **4**, and aryl iodides **2a-c,e-g** under Heck conditions ($PdCl_2(PPh_3)_2$, NEt_3, DMF or MeCN, 80°C) (see Scheme and Table 2).

Table 2.- Heck reaction between ethyl acrylate, **4**, and *para*-substituted aryl iodides **2**.

Run	**2**, X	**4/2**/NEt_3/ $PdCl_2(PPh_3)_2$	[**4**] (M)	[**2**] (M)	Solvent/t(hours)[a]	**5**, %[b]	mp (C)
1	**2a**, MeO	1/1/2/0.06	0.28	0.28	MeCN/24	**5a**, 84	47-48[c]
2	**2b**, AcNH	1/1/2/0.05	0.38	0.38	DMF/24	**5b**, 61	131-132
3	**2c**, Me	2/1/2/0.05	0.85	0.43	MeCN/1	**5c**, 82	oil[d]
4	**2e**, Br	1.5/1/2/0.02	1.00	0.67	MeCN/1	**5e**, 42[e]	oil[f]
5	**2f**, MeCO	1.5/1/2/0.025	0.41	0.27	DMF/24	**5f**, 54	40-42[g]
6	**2g**, F_3C	1.5/1/2/0.03	0.37	0.25	MeCN/48	**5g**, 98	31-32

[a] All the reactions were performed at 80 C. [b] Isolated yields. All compounds showed spectroscopic behaviour as expected and correct elemental analysis when required. [c] Lit.[15] mp 45-46C. Lit. [16] mp 48.9-49.7C. [d] Lit. [15] bp 163-165C/25 mm Hg. [e] Ethyl 3-(4-(2-ethoxycarbonylvinyl)phenyl)propenoate (22%) was also isolated. [f] Aldrich catalogue: bp 180C/18 mm Hg. [g] Lit.[15] bp 205-207 C/30 mm Hg.

para-Substituted ethyl cinnamates **5** were treated with excess of iodobenzene, **2d**, under Jeffery-Larock conditions ($Pd(OAc)_2$, $NaHCO_3$, *n*-Bu_4NBr, DMF) to afford the *cis* isomers **6a-c,e-g** as major products (see Scheme and Table 3).

Table 3.- Heck reaction between *para*-substituted ethyl cinnamates **5** and phenyl iodide, **2d**.

Run	**5**, X	**5/2d**/$Pd(OAc)_2$/ $NaHCO_3$/*n*-Bu_4NBr	[**5**] (M)	T (C)/ t (days)[a]	% yield[b]	**6/3**[c]	mp (C) of **6**
1	**5a**, MeO	1/2/0.10/2.5/1.1	0.16	80/5	71 (80)	82/18	oil[d]
2	**5a**, MeO	1/2/0.10/2.5/1.1	0.29	60/5	47 (59)	98/2	oil[d]
3	**5a**, MeO	1/1/0.10/2.5/1.1	0.16	60/8	38 (45)	96/4	oil[d]
4	**5b**, AcNH	1/1.5/0.06/2.0/0.8	0.20	60/7	63	80/20	113-115[e]
5	**5c**, Me	1/2/0.10/2.5/1.1	0.12	80/4	63 (72)	78/22	oil[d]
6	**5c**, Me	1/2/0.10/2.5/1.1	0.17	60/6, then 80/2	66	89/11	oil[d]
7	**5c**, Me	1/1/0.10/2.5/1.1	0.26	60/8	47 (60)	92/8	oil[d]
8	**5e**, Br	1/2.2/0.10/2.5/1.1	0.26	60/3	68	96/4	60-62
9	**5f**, MeCO	1/2/0.10/2.5/1.1	0.23	100/3	100	60/40	oil[f]
10	**5g**, F_3C	1/2/0.10/2.5/1.1	0.27	100/3	75 (98)	75/25	49-50

[a] DMF as solvent in all cases. [b] Overall isolated yields. In brackets the yields with respect to non recovered alkene **5**. [c] Ratio of isomers calculated by ^{1}H-NMR integration. They were separated by column chromatography. All compounds showed spectral behaviour as expected and correct elemental analysis when required. [d] Described as an oil in the lit.[8] Spectral data are coincident. [e] Lit.[12] mp 141-143C for a compound of undetermined stereochemistry. [f] Pure samples of isomer **6f** could not be obtained.

Isomerization also occurs in a variable extent, being temperature dependent (in Table 3 compare runs 1 and 2; runs 5, 6 and 7). Cacchi[8] has also found a similar phenomenon in the reaction of 4-(*p*-hydroxyphenyl)butenone with a vinylic triflate.

Structural assignment of *E* and *Z* isomers was corroborated by NMR techniques (2D ^{1}H-^{13}C HMQC and 2D ROESY) on a 3:1 mixture of **3a/6a** and inferred in the rest of the cases.

In summary, the *cis* and *trans* isomers of β,β-diarylacrylates can be prepared stereospecifically by Heck reaction provided that control of the temperature is made to prevent extended isomerization of the initially formed alkene.

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