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Highly Stereoselective Preparation of 3,3-Disubstituted Acrylates on Polyethylene Glycol

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Abstract:

The highly stereoselective preparation of sterically hindered (*E*) and (*Z*)-3,3-diaryl acrylic acid esters using a parallel synthesis approach is described. The liquid phase reaction utilises polyethylene glycol monomethyl ether 5000 (mPEG 5000) as a soluble polymeric support and phase-transfer agent.

Keywords: Stereoselection; Polymer support; Heck reactions; Wadsworth-Emmons reactions

The palladium mediated coupling reaction of aryl and vinyl halides with olefins (Heck reaction) constitutes an important tool in organic synthesis [1]. Recently, we demonstrated the palladium catalysed vinylation of polyethylene glycol (PEG)-bound arylic halides [2] in liquid phase synthesis [3]. Preparations of trisubstituted olefins have been rarely investigated [4, 5]. Herein, we report the liquid phase parallel synthesis of *ortho*-, *meta*- and *para*-substituted 3,3-diaryl acrylic acids *via* a sequence of (*E*)-stereoselective Wadsworth-Emmons and highly stereoselective Heck reactions. Diethylphosphonoacetic acid esterified with polyethylene glycol 5000 monomethyl ether (mPEG 5000) was prepared in 93% yield following literature procedures [6, 7]. Mild and highly stereoselective (*E*)-olefination of **1** was accomplished with DBU and LiCl [8]. Quantitative arylation of the polymer-bound 3-substituted acrylic acids **2a-f** was obtained at 145°C under Jeffery-Larock conditions ($Pd(OAc)_2$, $NaHCO_3$, *n*-Bu_4NBr, DMF, Δ) [9] to give **4a-n**, but *n*-Bu_4NBr detrimentally affected the purification of the polymer *via* the precipitation method [3]. We found that no additional phase-transfer agent was necessary for the synthesis of **4a-n**. Due to the intrinsic autocatalytic properties of the PEG-bound starting material, the esterified PEG was utilised as combined polymeric support and phase-transfer agent [2, 10]. Increasing isomerisation of the initially stereodefined alkene at higher temperatures has been reported in Heck reactions, especially if electron-donating substituents are present [5]. Surprisingly, we found that the diastereomeric ratio of starting mPEG esters **2a-f** was essentially maintained in many cases during the Heck reaction even under prolonged heating (3d) at 145°C. Under these conditions highly stereoselective reactions were observed with an *ortho*-substituent present in 3-aryl acrylates **2a-e**. The Heck reaction of **2a** with three different aryl iodides predominantly resulted in the Z-products, as indicated by NOESY measurements. Even higher stereoselectivity was observed with the sterically hindered 1-naphthyl- (**2b**), 2-tolyl- (**2c**), and 2,4-dichlorophenyl- (**2d**) substituted acrylic acids. ^{1}H-NMR measurements indicated identical ratios of diastereoisomers of the Heck products and the corresponding starting materials **2b-d**. Acrylates without *ortho*-

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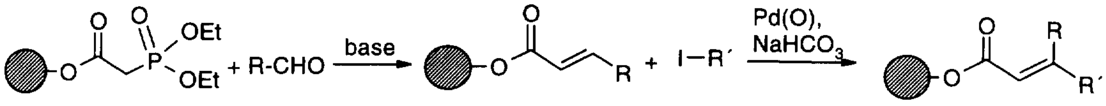
substituent (**2e**, **2f**) still showed some stereoselectivity in the Heck reaction, but a *Z*/*E* ratio of 83/17 could not be exceeded.

Table 1: Stereoselective Synthesis of 3,3-diaryl acrylic acid esters [3]



1 **2a-f** **3** **4a-n**

Entry	2	-R	-R′	4	Z/E Ratio[a]	Yield of **4** [%]
1	**2a**	2-Methoxyphenyl	4-Tolyl	**4a**	98/2	91
2	**2b**	1-Naphthyl	4-Tolyl	**4b**	>99/1	89
3	**2c**	2-Tolyl	4-Tolyl	**4c**	>99/1	94
4	**2d**	2,4-Dichlorophenyl	4-Tolyl	**4d**	>99/1	93
5	**2e**	4-Pyridyl	4-Tolyl	**4e**	74/26	82
6	**2a**	2-Methoxyphenyl	4-n-Butylphenyl	**4f**	99/1	94
7	**2c**	2-Tolyl	4-n-Butylphenyl	**4g**	<1/99	98
8	**2d**	2,4-Dichlorophenyl	4-n-Butylphenyl	**4h**	>99/1[c]	92
9	**2f**	Cyclopropyl	4-n-Butylphenyl	**4i**	17/83	95
10	**2a**	2-Methoxyphenyl	4-Methoxyphenyl	**4j**	98/2[c]	94
11	**2b**	1-Naphthyl	4-Methoxyphenyl	**4k**	<1/99	95
12	**2c**	2-Tolyl	4-Methoxyphenyl	**4l**	<1/99	94
13	**2d**	2,4-Dichlorophenyl	4-Methoxyphenyl	**4m**	>99/1	88
14	**2e**	4-Pyridyl	4-Methoxyphenyl	**4n**	83/17	89

[a] The *Z*/*E* ratios refer to the Heck reaction only and are corrected by the *Z*/*E* ratios of the starting acrylic acids 2a-f. For >99/1, exclusively the (*Z*)-isomer and for <99/1 exclusively the (*E*)-isomer was detected by ^{1}H-NMR. [b] Confirmed by NOESY experiments.

We assumed that the polymeric support additionally improved the stereoselectivity of the Heck reaction. Thus, isomerically pure (*E*)-2-methoxyphenyl acrylic acid methyl ester (as indicated by ^{1}H-NMR) was conventionally reacted with 4-iodo toluene under identical Heck conditions (2.5 eq. Bu_4NBr, 145°C, 20h). The relative *Z*/*E* ratio of the so obtained 3-(2-methoxyphenyl)-3-(4-tolyl)-acrylic acid methyl ester was 90/10 *versus* a *Z*/*E* ratio of 98/2 of the polymer-bound product (**4a**, entry 1). This result, indeed, indicates an influence of the mPEG 5000 support.

[3] **Representative Heck Reaction** (**4a**, entry 1): To 1g **2a** in 5 ml DMF 4-methoxyiodobenzene (234 mg, 1 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) and $NaHCO_3$ (42 mg, 0.5 mmol) were added under argon and stirred at 145°C for 20h. The mixture was centrifuged, the liquid precipitated into 80 ml ice cold MTBE and centrifuged again. The polymer was re-dissolved in 5 ml CH_2Cl_2 and the precipitation step repeated twice. White crystals. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 5.00 Hz, 1H), 7.28-6.96 (m, 5H), 6.82 (d, J = 8.74 Hz, 2H), 6.19 (s, 1H), 4.12 (t, J = 4.13 Hz, 2H), 3.81-3.51 (m, PEG), 3.38 (s, 3H). Yield: 91%.

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