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Brief Report

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A Simple Metal-Ligand Catalyzed Heck-Type Reaction for β, β-Doublearylation of Acrylic Acid Esters

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Introduction

As a part of Pd-catalyzed reactions the Heck-Mizoroki reaction has a huge significance in R&D of pharmaceuticals [1]. Since the very first steps in the discovery of this reaction type, double arylation of acrylic esters have been known, but just recently investigated in greater detail. In most cases β,β-diarylated acrylates were obtained under demanding conditions such as high pressure [2], special metal-ligand systems [3], ionic liquids [4] or special auxiliary reactants [5]. Double arylation has also been observed in microwave reactions [6]. By using propenols as starting material double arylation could be achieved in a domino Heck isomerization/Saegusa/Heck reaction resulting in β,β-diarylated propenals [7]. Yet no study focused on the basic conditions that were already used in the very first years after discovering this reaction type. Going back to its origins, we developed a simple and straightforward procedure that uses a basic metal-ligand system to synthesize β,β-diarylated acrylates and gives access to a pharmaceutical interesting class of products that is usually received under harsh conditions and in bad yields.

Keywords: Alkenes; Catalysis; One-pot Synthesis

General Procedure

Methyl acrylate (600 mg, 6.97 mmol), aryl iodide (27.9 mmol, 4 eq), potassium carbonate (2.12g, 15.3 mmol), palladium acetate (78.2 mg, 348 µmol) and tri-o-tolylphosphine (212 mg, 697µmol) are dissolved in dimethylformamide (5 ml) and stirred for 3 hours at 70˚C. Then the mixture is stirred for 72 hours at 110˚C. Ethyl acetate (30 ml) is added, the solution washed with brine (15 ml) and water (15 ml) and the organic layer is dried with sodium thiosulfate. The solvent is removed under reduced pressure and the product is obtained after column chromatography on silica gel (hexane/ethylacetate 20:1 v/v).

3,3-Di-p-tolylmethylacrylate (2a)

Yield: 562.7 mg, yellow oil

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.23 (dd, J = 8.0, 3.9 Hz, 4H), 7.15 (dd, J = 7.7, 5.6 Hz, 4H),6.35 (s, 1H), 3.65 (s, 3H), 2.43 (s, 3H), 2.39 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 166.62 (s), 157.43 (s), 139.70 (s), 138.40 (s), 138.04 (s),136.05 (s), 129.25 (s), 129.14 (s), 128.64 (s), 128.43 (s), 115.66 (s), 51.19 (s), 21.47 (s), 21.30 (s).

MS (70 eV, EI): m/z (%) = 266.1 (100), 235.1 (98), 219.1 (6), 207.1 (26), 191.1 (40), 178.1 (13), 165.1 (18), 119.1 (33), 91.1 (13)

3,3-Di-m-tolylmethylacrylate (2b)

Yield: 527.4 mg, colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 1H), 7.26 – 7.14 (m, 4H), 7.08 (dd, J = 24.4,7.5 Hz, 2H), 7.03 (s, 1H), 6.36 (s, 1H), 3.64 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 166.54 (s), 157.50 (s), 145.12 (s), 141.08 (s), 138.94 (s),138.06 (s), 137.46 (s), 131.20 (s), 130.27 (s), 129.66 (s), 129.02 (s), 128.92 (s), 128.32 (s),127.77 (s), 126.36 (s), 125.71 (s), 116.71 (s), 51.25 (s), 21.53 (s), 21.47 (s).

MS (70 eV, EI): m/z (%) = 266.1 (94), 235.1 (100), 219.1 (9), 207.1 (62), 192.1 (53), 178.1(16), 165.1 (24), 115.1 (38), 89.1 (14)

3,3-Di-o-tolylmethylacrylate (2c)

Yield: 134 mg, colourless oil.

^{1}H-NMR (500 MHz, CDCl3): δ = 7.32 – 7.13 (m, 8H), 6.21 (s, 1H), 3.67 (s, 3H), 2.40 (s, 3H),2.22 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 166.20 (s), 156.83 (s), 140.80 (s), 139.42 (s), 135.77 (s),135.60 (s), 131.30 (s), 130.18 (s), 129.92

(s), 129.21 (s), 128.45 (s), 128.05 (s), 125.86 (s),125.33 (s), 121.64 (s), 51.35 (s), 20.93 (s), 19.96 (s).

MS (70 eV, EI): m/z (%) = 266.1 (12), 251.1 (42), 235.1 (100), 219.1 (19), 205.1 (41), 191.1(99), 178.1 (45), 165.1 (28), 115.1 (55), 91.1 (23)

3,3-Bis(4-methoxyphenyl) methylacrylate (2d)

Yield: 868.4 mg, yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.95 – 6.89 (m,2H), 6.88 – 6.82 (m, 2H), 6.25 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 166.73 (s), 160.85 (s), 159.76 (s), 156.85 (s), 133.84 (s),130.90 (s), 130.03 (s), 114.30 (s), 113.76 (s), 113.26 (s), 55.33 (s), 55.19 (s), 51.09 (s).

MS (70 eV, EI): m/z (%) = 298.1 (100), 267.1 (59), 240.1 (17), 225.1 (27), 209.1 (10), 195.1(8), 181.1 (10), 165.1 (15), 152.1 (26), 135.1 (51)

3,3-Bis(3-methoxyphenyl) methylacrylate (2e)

For this derivate 300 mg (3.48 mmol) of methyl acrylate were used as educt.

Yield: 234 mg, yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.32 – 7.28 (m, 1H), 7.24 (t, J = 8.0 Hz, 1H), 6.93 (dd, J =2.6, 0.9 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.87 – 6.84 (m, 1H), 6.83 – 6.80 (m, 1H), 6.76 (dd, J =2.5, 1.6 Hz, 1H), 6.37 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.62 (s, 3H).

$_{13}$C-NMR (126 MHz, CDCl3): δ = 166.38 (s), 159.64 (s), 159.29 (s), 156.48 (s), 142.11 (s),140.16 (s), 129.42 (s), 128.99 (s), 121.65 (s), 120.93 (s), 117.22 (s), 114.95 (s), 114.78 (s),114.07 (s), 113.80 (s), 55.36 (s), 55.29 (s), 51.35 (s).

MS (70 eV, EI): m/z (%) = 300.1 (3), 298.1 (100), 267.1 (71), 239.1 (59), 224.1 (24), 208.1(11), 195.1 (11), 181.1 (16), 165.1 (27), 152.1 (33), 135.1 (21)

3,3-Bis(4-chlorophenyl) methylacrylate (2f)

Yield: 898 mg, yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.19 (d, J= 8.8 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.33 (s, 1H), 3.62 (s, 3H).

MS (70 eV, EI): m/z (%) = 309.0 (9), 308.0 (45), 306.0 (68), 277.0 (65), 275.0 (100), 247.0 (20), 212.0 (78), 176.1 (70), 139.0 (24)

3,3-Bis(3-chlorophenyl) methylacrylate (2g)

Yield: 433 mg, yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.38 (ddd, J = 8.1, 2.0, 1.3 Hz, 1H), 7.35 (ddd, J = 7.4, 2.2,1.1 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.27 (t, J = 4.6 Hz, 1H), 7.19 (t, J = 1.7 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.10 (dt, J = 7.4, 1.4 Hz, 1H), 6.37 (s, 1H), 3.64 (s, 3H).

$_{13}$C-NMR (126 MHz, $CDCl_3$): δ = 165.80 (s), 153.89 (s), 142.08 (s), 139.96 (s), 134.80 (s),134.20 (s), 129.89 (s), 129.78 (s), 129.46 (s), 129.12 (s), 128.72 (s), 128.24 (s), 127.41 (s),126.49 (s), 118.82 (s), 51.59 (s), 31.70 (s), 22.77 (s), 14.22 (s).

MS (70 eV, EI): m/z (%) = 309.0 (10), 308.0 (44), 306.0 (67), 277.0 (66), 275.0 (100), 247.0 (35), 212.0 (97), 176.1 (87), 139.0 (16)

1.1. 3,3-Bis(4-fluorophenyl) methylacrylate (2h)

Yield: 167 mg, yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26 (dd, J = 9.0, 5.3 Hz, 2H), 7.18 (dd, J = 8.8, 5.4 Hz, 2H),7.08 (t, J = 8.7 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 6.31 (s, 1H), 3.62 (s, 3H).

$_{13}$C-NMR (126 MHz, CDCl3): δ = 166.27 (s), 164.75 (s), 163.92 (s), 162.75 (s), 161.95 (s),155.04 (s), 143.64 (s), 136.99 (d, J = 2.9 Hz), 134.50 (d, J = 3.2 Hz), 131.21 (s), 131.15 (s),130.34 (s), 130.28 (s), 130.08 (s), 130.01 (s), 117.06 (s), 115.72 (s), 115.54 (s), 115.28 (s),115.11 (s), 51.41 (s).

MS (70 eV, EI): m/z (%) = 274.1 (77), 243.1 (100), 214.1 (72), 194.1 (30), 175.1 (15), 123.0 (27)

1.2. 3,3-Di(naphthalene-1-yl) methylacrylate (2i)

Yield: 164 mg, yellow oil.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.52 (dd, J = 8.3, 0.7 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.96 – 7.85 (m, 3H), 7.82 (dd, J = 5.9, 3.4 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.50 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 2H), 6.64 (s, 1H), 3.50 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 166.10 (s), 153.58 (s), 139.57 (s), 138.36 (s), 134.31 (s),133.70 (s), 131.42 (s), 130.87 (s), 129.22 (s), 128.86 (s), 128.67 (s), 128.61 (s), 127.25 (s),126.98 (s), 126.58 (s), 126.46 (s), 126.08 (s), 125.85 (s), 125.31 (s), 125.22 (s), 125.18 (s),125.11 (s), 124.36 (s), 60.47 (s), 51.41 (s), 21.13 (s), 14.31 (s).

MS (70 eV, EI): m/z (%) = 338.1 (19), 305.1 (12), 278.1 (100), 263.1 (11), 210.1 (23), 179.0(10), 152.1 (10), 138.1 (26)

3,3-Bis(3,4-dimethylphenyl) methylacrylate (2j)

Yield: 90.5 mg, yellow oil.

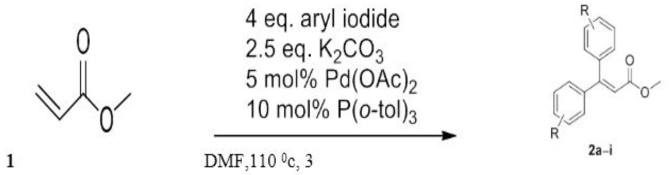
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, J = 7.6 Hz, 1H), 7.13 (s, 1H), 7.10 (d, J = 7.9 Hz,1H), 7.04 (dd, J = 7.9, 1.8 Hz, 1H), 6.99 (dd, J = 10.3, 2.6 Hz, 2H), 6.31 (s, 1H), 3.64 (s, 3H),2.33 (s, 3H), 2.29 (s, 2H), 2.28 (s, 3H), 2.26 (s, 2H).

^{13}C-NMR (126 MHz, CDCl3): δ = 166.73 (s), 157.84 (s), 139.01 (s), 138.37 (s), 136.64 (s),136.59 (s), 136.53 (s), 135.97 (s), 130.34 (s), 129.69 (s), 129.54 (s), 129.16 (s), 126.91 (s),126.24 (s), 115.50 (s), 51.19 (s), 31.71 (s), 22.77 (s), 19.87 (s), 19.79 (s), 19.68 (s), 14.21 (s).

MS (70 eV, EI): m/z (%) = 294.2 (100), 263.1 (81), 235.1 (25), 220.1 (29), 205.1 (25), 189.1(19), 133.1 (34)

Results and Discussion

This paper reports a simple metal-ligand catalyzed way to generate β,β-diarylated acrylic acids from standard chemicals. Moreno-Mañas, et al. showed the double arylation of ethyl cinnamates using similar conditions and a phase-transfer catalyst [8]. Unfortunately, this study only produced asymmetric ethyl 3-aryl-3-phenyl propenoates with para-substituted aryls. To get a wider view on this reaction, we varied the position of the substitutes and generated symmetric 3,3-diarylic esters. While usual ways to generate diarylated acrylic acids need complex ligands for the palladium, we used tri(*o*-tolyl) phosphine as ligand. As base potassium carbonate showed to have the best results yield-wise. The reaction was carried out in dimethylformamide and stirred for 3 days at 110 °C. The aryl iodides were used in excess and the unreacted aryl iodides were retrieved from the reaction mixture. The results are listed in (Table 1).



Entry	Aryl iodide	Product	Yield(%)
1	$4\text{-MeC}_6\text{H}_4\text{I}$	2a	30
2	$3\text{-MeC}_6\text{H}_4\text{I}$	2b	28
3	$2\text{-MeC}_6\text{H}_4\text{I}$	2c	7
4	$4\text{-MeOC}_6\text{H}_4\text{I}$	2d	42
5	$3\text{-MeOC}_6\text{H}_4\text{I}$	2e	23
6	$4\text{-ClC}_6\text{H}_4\text{I}$	2f	8
7	$3\text{-ClC}_6\text{H}_4\text{I}$	2g	20
8	$4\text{-FC}_6\text{H}_4\text{I}$	2h	9
9	$\text{C}_{10}\text{H}_7\text{I}$	2i	7
10	$3,4\text{-Me}_2\text{C}_6\text{H}_3\text{I}$	2j	4

Table 1: Doublearylation of acrylic esters via Heck reaction.

The highest yields were achieved by using methyl acrylic esters, benzyl and tert-butyl esters did only produce the monoarylated products. The equivalents for the aryl halides were raised from 2 equivalents up to 4 equivalents, where no yield improvement was observed above this amount. Potassium carbonate proved to be a better choice for the base than trimethylamine and tri(*o*-tolyl) phosphine showed to be the ligand of choice in comparison to triphenylphosphine and dppe.

Electron deficient aryl halides such as iodopyridin or 3-chloro-4-iodobenzotrifuoride only delivered the monoarylated product. Depending on the substitution pattern, the yield was highest for para-substituted and lowest for ortho-substituted aryl halides. Most ortho-substituted aryl halides only produced the monoarylated product.

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