An efficient metal-ligand catalyzed Heck-type reaction for β,β-double arylation of acrylates

Abstract

The Heck-Mizoroki reaction was further developed into a straightforward and efficient 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 obtained under considerably harsher conditions and worse yields.

Keywords: alkenes, catalysis, one-pot synthesis, microwave reactions, Heck-Mizoroki reaction, tri(o-tolyl)phosphine

Introduction

As a part of Pd-catalyzed reactions the Heck-Mizoroki reaction has a huge significance in R&D of pharmaceuticals. 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, special metal-ligand systems, ionic liquids or special auxiliary reagents. Double arylation has also been observed in microwave reactions. 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. 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.

General procedure

Methyl acrylate (600mg, 6.97mmol), aryl isocyanate (27.9mmol, 4eq), potassium carbonate (2.12g, 15.3mmol), palladium acetate (78.2mg, 0.15mol%), potassium tri(o-tolyl)phosphine (37.7mg, 0.15mol%) and tri(o-tolyl)phosphine (212mg, 0.62mmol) are dissolved in dimethylformamide (5ml) and stirred for 3hours at 70°C. Then the mixture is stirred for 72hours at 110°C. Ethyl acetate (30ml) is added, the solution washed with brine (15ml) and water (15ml) 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 20:1v/v).

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

Yield: 562.7mg, yellow oil: 1H-NMR (500MHz, CDCl3): 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), 6.34 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H).

C-NMR (126MHz, CDCl3): δ=166.20 (s), 156.83 (s), 140.80 (s), 139.24 (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), 21.53 (s), 21.47 (s).

M.S (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-tolymethylacrylate (2b)

Yield: 527.4mg, colourless oil: 1H-NMR (500 MHz, CDCl3): 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), 6.34 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H).

C-NMR (126MHz, CDCl3): 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).

M.S (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-tolymethylacrylate (2c)

Yield: 134mg, colourless oil: 1H-NMR (500MHz, CDCl3): δ=7.32–7.13 (m, 8H), 6.21 (s, 1H), 3.67 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H).

C-NMR (126MHz, CDCl3): 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).

M.S (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: 868.4mg, yellow oil: 1H-NMR (500MHz, CDCl3): 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).

C-NMR (126MHz, CDCl3): 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).

M.S (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 300mg (3.48mmol) of methyl acrylate were used as educt.
**Yield: 234mg, yellow oil:** $^1$H-NMR (500MHz, CDCl$_3$): $\delta$=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 (126MHz, CDCl$_3$): $\delta$=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: 433mg, yellow oil:** $^1$H-NMR (500MHz, CDCl$_3$): $\delta$=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 (126MHz, CDCl$_3$): $\delta$=165.80 (s), 153.89 (s), 142.08 (s), 139.96 (s), 134.40 (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 (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(3,4-dimethylphenyl)methylacrylate (2g)**

**Yield: 433mg, yellow oil:** $^1$H-NMR (500MHz, CDCl$_3$): $\delta$=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 (126MHz, CDCl$_3$): $\delta$=166.27 (s), 164.75 (s), 163.92 (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 (%)=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)

**Conclusion**

This study reports a simple as efficient metal-ligand catalyzed way to generate β,β-diazyrted acrylic acids from standard chemicals. Moreno-Mañas et al. showed the double arylation of ethyl cinnamates using similar conditions and a phase-transfer catalyst. Unfortunately, this study only produced asymmetric ethyl 3-aryl-3-phenyl propanoates with para-substituted aryls. To get a wider variety on this reaction, we varied the position of the substitutes and generated symmetric 3,3-diaryl esters. While usual ways to generate diazyrted acrylic acids need complex ligands for the palladium, we generated symmetric 3,3-diarylic esters.

**Table 1 Double arylation of acrylic esters via Heck reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>4-MeC$_3$H$_7$</td>
<td>2a</td>
<td>30</td>
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<tr>
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<td>3-MeC$_3$H$_7$</td>
<td>2b</td>
<td>28</td>
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<td>3</td>
<td>2-MeC$_3$H$_7$</td>
<td>2c</td>
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<td>2d</td>
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<tr>
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<td>23</td>
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<tr>
<td>6</td>
<td>4-CIC$_3$H$_7$</td>
<td>2f</td>
<td>8</td>
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<tr>
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<td>8</td>
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<td>9</td>
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<tr>
<td>9</td>
<td>C$_6$H$_5$I</td>
<td>2i</td>
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<tr>
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<td>3,4-Me$_2$C$_6$H$_4$I</td>
<td>2j</td>
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</table>

Citation: Wolff B, Meyer-Almes FJ. An efficient metal-ligand catalyzed Heck-type reaction for β,β-double arylation of acrylates. MOJ Biorg Chem. 2019;3(1):27–29. DOI: 10.15406/mojboc.2019.03.00094
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) phosphate showed to be the ligand of choice in comparison to triphenylphosphine and dppe. Electron deficient aryl halides such as iodoxyridin or 3-chloro-4-iodobenzotrifluoride only delivered the monoarylated product. Depending on the substitution pattern, the yield was highest for para-substituted and lowest for ortho-substituted ary1 halides. Most ortho-substituted ary1 halides only produced the monoarylated product.

Acknowledgments

None.

Conflicts of interest

There exists no conflict of financial or any other interest.

References