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HAL Id: hal-03118824
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Submitted on 22 Jan 2021

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Solvent-free synthesis of unsaturated amino esters in a ball-mill
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A B S T R A C T

The ball-milling technique was used under solvent-free conditions to perform a Horner–Wadsworth–Emmons reaction in the presence of a mild carbonate base. Starting from a phosphonate-substituted glycine, this method gave access to Boc-protected unsaturated amino esters in excellent yield and selectivity in many cases. The scope of the reaction was delineated.

Keywords:
Ball-mill
Solvent-free
Amino acid
Horner–Wadsworth–Emmons
Olefination
Dehydroalanine
Carbonate base
Phosphonate

Ball-milling is a mechanochemical technique that is widely applied to the grinding of minerals into fine particles, to the preparation, and modification of inorganic solids.1,2 Ball-mill chemistry is of interest because it is performed in the absence of solvent, under environmentally friendly conditions. In the last years, this technique has found interest in synthetic organic chemistry.3,4 The reported examples include nitrone synthesis,5 functionalization of fullerenes,6 reductive benzylation of malonitrile,7 protection of amines,8 Knoevenagel reaction,9 aldol condensation10 and its asymmetric version,11 Michael additions,9 preparation of phosphorus ylides,12 oxidative coupling of 2-naphthol,13 Heck,14 Suzuki15 and Sonogashira16 coupling reactions, and peptide synthesis.17

One powerful method for making carbon–carbon bond is the Wittig reaction starting from carbonyl compounds and making use of a phosphorus ylide.18 It was shown recently that this reaction could be performed in a ball-mill12 (scheme 1).

The Horner–Wadsworth–Emmons (HWE) version19 of the Wittig reaction focuses on the use of more stabilized phosphonate ylides. This is a method of choice for the preparation of unsaturated esters (EWG = CO2R). Usually, the phosphonate stabilized carbanion is sufficiently nucleophilic to react under mild conditions to yield the olefin. As part of our program to prepare unnatural amino acids and use them as building blocks for peptide synthesis,20 we considered the development of a HWE reaction in a ball-mill as a valuable route for the synthesis of unsaturated amino esters.21 The synthesis developed by Schmidt et al.,22 based on the HWE reaction, is a practical method for making olefinic amino esters from a carbonyl compound and a phosphonate derivative of glycine (scheme 2). Nevertheless, it requires usually the use of an excess of organic base and a low temperature for the deprotonation step is needed.

Few examples of solvent-free HWE reactions have been published but very often an excess of liquid reactant serves as the solvent.23a–c Since the Wittig reaction has been explored under mechanical activation,12 we presumed that the HWE version could be a viable and powerful approach for the preparation of unsaturated amino esters starting from carbonyl compounds.

Scheme 1. Solvent-free Wittig reaction in a ball-mill.

Aromatic aldehydes (entries 1–6) reacted efficiently with complete conversion in most of the cases. Even a hindered ortho-substituted aryl aldehyde, such as 2b (entry 2), gave an excellent result. For this series, the Z/E selectivity was very high since only the Z isomer could be detected, except in the case of naphthaldehyde 2f (entry 6) where the proportion is in favor of the same isomer but with a lower selectivity. Even if reaction conditions were tested on the formation of 3a, starting from solid aldehyde 2a (entry 1), liquid aldehydes also gave satisfactory results (entries 3–6). Among the aliphatic aldehydes (entries 7–10), n-butyraldehyde 2g, a linear aldehyde, gave the best results in terms of yields and selectivity (entry 7). Conversions of mono-substituted methanals 2h and 2l (entries 8 and 9) were very good but the selectivity was poor. t-Butyraldehyde 2j, most probably too hindered, was not very reactive and full conversion could not be obtained. Finally, the two ketones 2k and 2l which were tried in this reaction were unreactive. The HWE reaction of ketones for the synthesis of tetra-substituted alkenes is a more demanding process due to the steric hindrance involved between the two reactants, especially in the present study for the preparation of dehydro amino esters. In solution in the presence of sodium hydride, as stated by Schmidt et al., ketones are unreactive unless activated. Better results were obtained with DBU. In the ball-mill, only di- and tri-substituted olefins were encountered on a solid aldehyde, such as 2b (entry 2) gave a good result. Better results were obtained with DBU. In the ball-mill, only di- and tri-substituted olefins were obtained. In this reaction, only one isomer was obtained and characterized by 1H and 13C NMR. In contrast to the Wittig reaction in a ball-mill, the stereoschemical outcome of the reaction in the ball-mill is the same as in solution. Only the Z isomer could be detected by NMR.

To investigate the scope of the reaction with various aldehydes and ketones, we considered their reactions in the presence of Cs2CO3 or K2CO3. Cs2CO3 was considered as the best base but since K2CO3 gave satisfactory results, it was also tested because of its superior ability from an economical, ecological, and toxicological point of view. Eventually, it proved even superior to Cs2CO3 in many cases. The preparation of various protected amino esters is presented in Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO3 (3)</td>
<td>5</td>
<td>n.d.*</td>
</tr>
<tr>
<td>2</td>
<td>K2CO3 (1)</td>
<td>91</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>K2CO3 (3)</td>
<td>93</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>KOH (3)</td>
<td>94b</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>Cs2CO3 (2)</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Cs2CO3 (3)</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>Cs2CO3 (1.5)</td>
<td>94</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>DBU</td>
<td>63</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

* Starting materials were ground in a planetary ball-mill for 7 h.

b Hydrolysis product 4a was also obtained.

c n.d.: not determined.
### Table 2
Synthesis of amino esters in a ball-mill

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Physical state</th>
<th>mp (°C)</th>
<th>Base</th>
<th>Conversion (%)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Z/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>Solid</td>
<td>44–48</td>
<td>Cs₂CO₃</td>
<td>100</td>
<td>3a</td>
<td>95</td>
<td>100/0</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>Solid</td>
<td>16–19</td>
<td>K₂CO₃</td>
<td>96</td>
<td>3b</td>
<td>85</td>
<td>100/0</td>
</tr>
<tr>
<td>3</td>
<td>N=CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3c</td>
<td>88</td>
<td>100/0</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3d</td>
<td>82</td>
<td>100/0</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>Cs₂CO₃</td>
<td>100</td>
<td>3e</td>
<td>89</td>
<td>100/0</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3f</td>
<td>76</td>
<td>82/18</td>
</tr>
<tr>
<td>7</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3g</td>
<td>80</td>
<td>100/0</td>
</tr>
<tr>
<td>8</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3h</td>
<td>61</td>
<td>66/44</td>
</tr>
<tr>
<td>9</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>100</td>
<td>3i</td>
<td>90</td>
<td>61/39</td>
</tr>
<tr>
<td>10</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>35</td>
<td>3j</td>
<td>n.d.</td>
<td>100/0</td>
</tr>
<tr>
<td>11</td>
<td>CHO</td>
<td>Solid</td>
<td></td>
<td>K₂CO₃</td>
<td>0</td>
<td>3k</td>
<td>0</td>
<td>0–</td>
</tr>
<tr>
<td>12</td>
<td>CHO</td>
<td>Liquid</td>
<td></td>
<td>K₂CO₃</td>
<td>0</td>
<td>3l</td>
<td>0</td>
<td>0–</td>
</tr>
</tbody>
</table>

### Acknowledgments

We thank the MESR, the CNRS and Idenix Pharmaceuticals (fellowship to A.B.) for their financial support.

### References and notes


24. All new compounds were characterized by ¹H and ¹³C NMR, mass spectrometry, and high resolution mass spectrometry.

25. Procedure for the preparation of (Z)-methyl 2-[(tert-butoxycarbonyl)amino]-3-(3,5-dimethoxyphenyl)acrylate 3a: methyl 2-[(tert-butoxycarbonyl)amino]-2-(dimethoxyphosphoryl)acrylate (157 mg, 0.53 mmol), 3,5-dimethoxybenzaldehyde (80 mg, 0.48 mmol) and cesium carbonate (314 mg, 0.96 mmol) were introduced in a 12 mL grinding jar with five stainless steel balls (7 mm diameter). The grinding jar was placed in a planetary ball-mill and stirred at 550 rpm during 7 h. EtOAc was added in the jar and the mixture was washed with water, dried over MgSO₄, concentrated under vacuo. The residue was filtered on a silica gel pad (eluent: cyclohexane/EtOAc, 1:1) to afford 165 mg of the titled compound (100%) as a white powder: mp 108–109°C; ¹H NMR (CDCl₃, Me₄Si) δ 1.30 (br s, 9H, C(CH₃)₃), 3.72 (s, 6H, 2OCH₃), 3.95 (s, 3H, OMe), 6.37 (t, J = 2.2 Hz, 1H, CH), 6.63 (d, J = 2.0 Hz, 2H, 2 × CH), 7.09 (1H, s, CH). ¹³C NMR (CDCl₃, Me₄Si) δ 28.10 (C(CH₃)₃), 52.62 (OCH₃), 55.32 (2OCH₃), 81.02 (C), 101.67 (CH), 107.46 (2CH), 125.18 (CH), 129.76 (C), 135.76 (C), 152.74 (C@O), 160.66 (2C), 165.96 (C@O); high resolution MS calcd for C₁₇H₂₄NO₆: 338.1604. Found: 338.1599 [M+H]+.