Amano PS catalysed methanolysis of maleimides: An efficient synthesis of methyl maleanilates\(^\dagger\)

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A first simple method for Amano PS catalysed methanolysis of maleimides 1a-f has been described to obtain methyl maleanilates 2a-f in 80-90\% yields.

Biotransformations involve the use of biological methods to effect chemical reactions and form a bridge between chemistry and biology. They are highly chemo-, regio- and enanti-selective in their action\(^1\) and are environment friendly\(^2\). Alkyl maleanilates 2a-g are important building blocks in the synthesis of several structurally interesting and biologically important heterocyclic systems\(^3\). Alkyl maleanilates 2a-g are generally prepared by the treatment of corresponding anilic acids with (i) alkanoil\(\text{HCl}(\text{gas})\), (ii) alkanoil\(\text{H}_{2}\text{SO}_{4}\), (iii) alkanoil\(\text{triethylamine}\), (iv) dialkyl sulphite\(^7\), (v) alkanoil\(\text{SOCl}_{2}\), (vi) alkanoil\(\text{P}_{2}\text{O}_{5}\), (vii) alkanoil\(\text{PCl}_{3}\), (viii) \(\text{CH}_{2}\text{N}_{2}\)\(^1\) and (ix) \(\text{NaOH}/\text{alkyl iodide}\)\(^8\). In these acid/base catalysed esterification reactions the possibility of amide bond cleavage is there, both in the starting material and the formed product, while the excess of diazomethane used can undergo Michael addition to form ester to yield cyclopropane derivative. Moreover these methods cannot be used directly (without protection) if acid/base sensitive functional groups are present in the substrate anilic acid. Preparation of esters is one of the most important reaction in organic chemistry and development of new simple, efficient, above said drawbacks free and environment friendly method will be useful. In this context, we herein report the first simple enzyme catalysed preparation of alkyl maleanilates 2a-g starting from corresponding cyclic imides 1a-g.

### Results and Discussion

The anilic acids on dehydration under thermodynamically controlled conditions (\(\text{Ac}_{2}\text{O}/\text{NaOAc}, \Delta\))

\(70^\circ\text{C}, 2\text{ hr})\)\(^9\) gave corresponding imides 1a-i in quantitative yields. The maleimides 1a-f in methanol underwent a smooth alcoholysis in the presence of catalytic amount of Amano PS (10\% by weight) at room temperature to yield corresponding esters 2a-f in more than 80\% yields (Scheme I, Table I). These reactions were monitored by TLC and the reaction of 1a was very fast and major reaction was over in 1 hr time. The reactions of substituted maleimides 1b-f were relatively slow and took 18 to 24 hr time for major completion. The reaction of maleimide 1g with ethanol and succinimide 1h with methanol were slow and the esters 2g and 2h were obtained only in 28\% and 31\% yields, respectively in 100 hr reaction time. The phthalimide 1i did not undergo the enzyme catalysed methanolysis to yield 2i under neutral reaction conditions, as the \(N\)-arylphthalimides are thermodynamically more stable than the corresponding phthalanic esters and the condition to obtain the esters of phthalanic acids is still elusive\(^9\).

### Conclusion

In summary, we have demonstrated the first simple and efficient enzymatic method for the synthesis of methyl maleanilates in 80-90\% yields. The present method may also be useful for alcoholysis of several
other imides, iso-imides and deamination of meso-cyclic anhydride derivatives.12

Experimental Section
Mps were taken in a Buchi melting point B-540 apparatus and are uncorrected. 1H NMR spectra were recorded in CDCl3 with TMS as an internal standard on a Bruker AC 200 NMR spectrometer (200 MHz). The FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. Column chromatographic separations were done on ACME silica gel (60-120 mesh). The starting imides were prepared using known procedure.13 Amano PS-800 U (Amano Pharmaceutica) was used. The activity of the lipase powder used is expressed in terms of units, 1 unit of enzyme powder.

General procedure for methanolysis of maleimides
To a stirred solution of maleimide (1a-f, 500 mg) in methanol (25 mL) was added Amano PS (50 mg) and the reaction mixture was stirred at rt (6 to 24 hr). The reaction mixture was filtered through sintered glass funnel, washed with methanol, concentrated in vacuo and silica gel column purification of the residue [elution with petroleum ether - ethyl acetate (85:15) mixture] furnished pure esters 2a-f in 80 to 90% yields. The esters 2g and 2h were also prepared similarly. The isolated enzyme was dried at rt and used for second conversion without any noticeable loss of activity.14

Analytical and spectral data for imides 1a-i and esters 2a-h
1a: mp 87 °C; IR (Nujol): 1770, 1709, 1600 cm−1; 1H NMR: 6.83 (s, 2H), 7.20-7.70 (m, 5H); 1b: mp 80-
81 °C; IR (Nujol): 1770, 1709, 1600 cm−1; 1H NMR: 2.16 (s, 3H), 6.87 (s, 2H), 7.05-7.20 (m, 1H), 7.20-
7.45 (m, 3H); 1c: mp 158 °C; IR (Nujol): 1770, 1709, 1605 cm−1; 1H NMR: 2.40 (s, 3H), 6.84 (s, 2H), 7.05-
7.25 (m, 3H), 7.36 (d, J = 6 Hz, 1H); 1d: mp 158 °C; IR (Nujol): 1770, 1709, 1605 cm−1; 1H NMR: 2.40 (s, 3H), 6.85 (s, 2H), 7.20 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H); 1e: mp 152-154 °C; IR (Nujol): 1769, 1709, 1607 cm−1; 1H NMR: 3.83 (s, 3H), 6.83 (s, 2H), 6.98 (d, J = 8 Hz, 2H), 12.46 (d, J = 8 Hz, 2H), 1f: mp 118-
20 °C; IR (Nujol): 1775, 1713, 1595 cm−1; 1H NMR: 6.87 (s, 2H), 7.32 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H); 1h: mp 158-60 °C; IR (Nujol): 1770, 1705, 1600 cm−1; 1H NMR: 2.38 (s, 3H), 2.87 (s, 4H), 7.15 (d, J = 6 Hz, 2H), 7.28 (d, J = 6 Hz, 2H), 1i: mp 210-12 °C; IR (Nujol): 1745, 1710, 1600 cm−1; 1H NMR: 2.41 (s, 3H), 7.31 (s, 4H), 7.70-8.10 (m, 4H); 2a: mp 76-77 °C; IR (Nujol): 3252, 1732, 1668, 1632, 1597 cm−1; 1H NMR: 3.85 (s, 3H), 6.22 (d, J = 12 Hz, 1H), 6.45 (d, J = 12 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 7.35 (t, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 10.85 (bs, 1H); 2b: mp 97-99 °C; IR (Nujol): 3217, 1730, 1665, 1641, 1600 cm−1; 1H NMR: 2.35 (s, 3H), 3.83 (s, 3H), 6.98 (d, J = 10 Hz, 1H), 6.94 (d, J = 10 Hz, 1H), 7.05-7.40 (m, 3H), 7.94 (d, J = 6 Hz, 1H), 10.20 (bs, 1H); 2c: mp 108-99 °C; IR (Nujol): 3304, 1732, 1666, 1614, 1595 cm−1; 1H NMR: 2.35 (s, 3H), 3.84 (s, 3H), 6.20 (d, J = 12 Hz, 1H), 6.43 (d, J = 12 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.40-7.60 (m, 2H), 10.70 (bs, 1H); 2d: mp 108-99 °C; IR (Nujol): 3283, 3250, 1726, 1670, 1636, 1607 cm−1; 1H NMR: 2.33 (s, 3H), 3.84 (s, 3H), 6.21 (d, J = 12 Hz, 1H), 6.44 (d, J = 12 Hz, 1H), 7.14 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 10.73 (bs, 1H); 2e: mp 58-60 °C; IR (Nujol): 3300, 1724, 1661, 1632, 1605 cm−1; 1H NMR: 3.80 (s, 3H), 3.84 (s, 3H), 6.20 (d, J = 12 Hz, 1H), 6.44 (d, J = 12 Hz, 1H), 6.88 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 10.68

Table 1 – Alcoholsysis of 1a-i to give the products 2a-i

<table>
<thead>
<tr>
<th>Compd</th>
<th>X</th>
<th>Ar</th>
<th>ROH</th>
<th>Time (hr)</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>1a</td>
<td>-CH=CH-</td>
<td>Phenyl</td>
<td>MeOH</td>
<td>6</td>
<td>2a</td>
<td>92</td>
</tr>
<tr>
<td>1b</td>
<td>-CH=CH-</td>
<td>a-Tolyl</td>
<td>MeOH</td>
<td>24</td>
<td>2b</td>
<td>81</td>
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<tr>
<td>1c</td>
<td>-CH=CH-</td>
<td>m-Tolyl</td>
<td>MeOH</td>
<td>18</td>
<td>2c</td>
<td>85</td>
</tr>
<tr>
<td>1d</td>
<td>-CH=CH-</td>
<td>p-Tolyl</td>
<td>MeOH</td>
<td>21</td>
<td>2d</td>
<td>88</td>
</tr>
<tr>
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<td>-CH=CH-</td>
<td>p-Anisyl</td>
<td>MeOH</td>
<td>24</td>
<td>2e</td>
<td>87</td>
</tr>
<tr>
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<td>24</td>
<td>2f</td>
<td>83</td>
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<td>100</td>
<td>2g</td>
<td>28</td>
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<tr>
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<td>p-Tolyl</td>
<td>MeOH</td>
<td>100</td>
<td>2h</td>
<td>31</td>
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<tr>
<td>1i</td>
<td>-O-C6H4-</td>
<td>p-Tolyl</td>
<td>MeOH</td>
<td>48</td>
<td>2i</td>
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</table>
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(bs, 1H); 2f: mp 98-100 °C; IR (Nujol): 3281, 3246, 1722, 1666, 1643, 1607 cm⁻¹; ¹H NMR: 3.86 (s, 3H), 6.24 (d, J = 12 Hz, 1H), 6.44 (d, J = 12 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 11.09 (bs, 1H); 2g: Thick oil; IR (Neat): 3306, 1726, 1666, 1635, 1607 cm⁻¹; ¹H NMR: 1.33 (t, J = 8 Hz, 3H), 2.32 (s, 3H), 4.29 (q, J = 8 Hz, 2H), 6.19 (d, J = 12 Hz, 1H), 6.42 (d, J = 12 Hz, 1H), 7.14 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 10.84 (bs, 1H); 2h: mp 103-04 °C; IR (Nujol): 3356, 1724, 1707, 1684, 1599 cm⁻¹; ¹H NMR: 2.30 (s, 3H), 2.55-2.90 (m, 4H), 3.70 (s, 3H), 7.10 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 7.64 (bs, 1H).

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References


