Maleic and phthalic anhydride condenses with amino acids and alkylamines under microwave irradiation to afford N-substituted maleimides and phthalimides in excellent yields.

Maleimides constitute an important class of chemically and biologically significant compounds. Reagents containing a maleimido ligand tethered to an active ester group are in high demand in modern chemistry and biotechnology. In addition, N-alkylphthalimides have received renewed interest as a source of functionalized β-lactams. In general, most methods of cyclic imide synthesis involve Lewis-acid-mediated condensation of an amine with maleic anhydride or n-alkylation of maleimide using Mitsunobu reaction conditions. Maleimide-linked esters are prepared by cyclo-condensation of maleimino acids in the presence of acetic carbonyl maleimide and amino acids. However, these methods have limitations of general applicability owing to low yield, extensive by-product formation and harsh reaction conditions.

There has been a growing interest in the use of microwave irradiation for heating in organic synthesis. This results in better selectivity, rate enhancement and reduction of thermally degradative products when compared with conventional heating. In addition, microwave-mediated synthesis without a solvent offers advantages for reducing hazardous explosions and the removal of high boiling aprotic solvents from the reaction mixture. Recently microwave irradiation has been utilized for N-alkylation of phthalimide in dry media under phase-transfer catalysis. Although the synthesis of N-arylmaleimides proceeds in excellent yields, the synthesis of N-alkylmaleimides under identical conditions is less satisfactory. In this report we describe a microwave-induced fast synthesis of potentially biologically active carboxyalkyl maleimides in a one-pot reaction by condensing functionalized amines with maleic anhydrides.

Equimolecular amounts of maleic anhydride (I) and amino acid (3, R2=H, Me, Ph; R3=CO2H, CO2Me) were placed in an open Erlenmeyer flask and heated in a domestic microwave oven for an appropriate time (Table 1) to obtain N-carboxyalkyl maleimides (4-6) in excellent yields (90-96%). Under identical conditions phthalic anhydride (2) reacted with alkylamine (3, R2=H, R3=Ph) and amino acids (3, R2=H, R3=CO2H) affording N-substituted phthalimides (9 and 10, respectively) in 89-95% yields. Interestingly, our procedure of microwave heating excludes polymerization. Further, alkylamines (3, R2=H, R3=Ph, vinyl) efficiently underwent one-pot condensation with I and 2, affording 7 and 8, respectively. All the products were identified by spectral and microanalytical analysis.

In conclusion we have described a microwave-mediated facile and fast synthesis of N-carboxyalkyl- and N-alkylmaleimides that may be biologically active. The reported one-pot procedure is economical because of its high selectivity, solvent-less condition and absence of dehydrating agent.

Experimental

Mps were uncorrected and recorded on a Buchi apparatus. IR spectra were obtained on a Perkin-Elmer 237B and 580B infra-red spectrometer in KBr discs. The 1H NMR spectra were recorded on a Varian T-60 and JEOL JNM FX90Q spectrometers using Me4Si as internal standard (δ/ppm). Mass spectra were recorded on a AEIMS-30 spectrometer at 70 eV. Microanalytical data were performed on a Perkin-Elmer Series II 2400 instrument. Reactions were conducted in a commercial microwave oven model ER 5054 D of Microwave Products (India) Ltd.

General Procedure.—A mixture of either maleic anhydride (1) or phthalic anhydride (2, 0.02 mol) and glycine (3, R2=H, R3=CO2H, 0.02 mol) was placed in an Erlenmeyer flask fitted with a loose top cap and heated in a commercial microwave oven operating at 2450 MHz by setting the power range to medium high (70% of total power). The reaction mixture turned red. After cooling, the reaction mixture was extracted with chloroform (2×30 ml) and washed with cold water (2×10 ml), dried (Na2SO4), filtered and the solvent removed.

N-CarboxymethyImaleimide 4: yield 94%, mp 112–13°C, C12H14N2O4 (M+ 237) 1 (KBr) 3040, 1720; 2 (CD3COCD3) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, methyl); 3 (KBr) 3010, 1710, 1725; 4 (CD3COCD3) 6.85 (s, 2 H, olefinic), 3.50 (1, 2 H, methylene); 5 (CDCl3) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, methyl); 6 (KBr) 3010, 1705, 1730.

N-(α-Carboxyethyl)maleimide 5: yield 90%, mp 97–98°C, C6H7NO4 (M+ 111) 2 (KBr) 3060, 1710, 1725; 3 (KBr) 3010, 1705, 1730; 4 (CD3COCD3) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, vinyl); 5 (CDCl3) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, vinyl).

N-(α-Methoxycarbonylbenzyl)maleimide 6: yield 95%, mp 87–89°C (lit.4b, 88°C); C12H14N2O4 (M+ 245) 1 (KBr) 3010, 1725, 1710; 2 (CDCl3) 7.25–8.25 (m, 5 H, aromatic), 6.90 (s, 2 H, olefinic), 4.85 (s, 1 H, methylene), 3.75 (s, 3 H, ester methyl); 3 (CDCl3) 6.70 (s, 2 H, olefinic), 4.85 (s, 1 H, methylene), 3.75 (s, 3 H, ester methyl); 4 (KBr) 3010, 1725, 1710; 5 (CDCl3) 7.20–7.40 (m, 5 H, aromatic), 6.70 (s, 2 H, olefinic); 6 (KBr) 3010, 1725; 7 (CDCl3) 6.70 (s, 2 H, olefinic), 4.85 (s, 1 H, methylene).

N-Benzylmaleimide 7: yield 96%, mp 69–70°C (lit.4b, 69–70.5°C); C12H14N2O4 (M+ 237) 1 (KBr) 3050, 1705; 2 (CDCl3) 7.20–7.40 (m, 5 H, aromatic), 6.70 (s, 2 H, olefinic), 4.68 (s, 2 H, methylene); 3 (CDCl3) 7.20–7.40 (m, 5 H, aromatic), 6.70 (s, 2 H, olefinic), 4.68 (s, 2 H, methylene); 4 (KBr) 3010, 1725.

N-Allylmaleimide 8: yield 82%, mp 42–43°C (lit.4b, 42.5–43°C); C12H14N2O4 (M+ 237) 1 (KBr) 3000, 1710; 2 (CDCl3) 6.72 (s, 2 H, olefinic), 5.80 (m, 1 H, vinyl), 5.12–5.24 (m, 2 H, vinyl), 4.10 (dt, 2 H, J 5.6 Hz, vinyl); 3 (CDCl3) 173 (M+).

N-Benzylphthalimide 9: yield 89%, mp 119–20°C (lit.4b, 118.5–119.5°C); C12H11NO4 (M+ 213) 1 (KBr) 3060, 1700; 2 (CDCl3) 7.65–7.88 (m, 4 H, aromatic), 7.20–7.45 (m, 5 H, aromatic), 4.80 (s, 2 H, olefinic); 3 (CDCl3) 7.20–7.45 (m, 5 H, aromatic), 4.80 (s, 2 H, olefinic); 4 (CDCl3) 161 (M+–CO2).

N-Carboxycarbonylmaleimide 10: yield 95%, mp 110–111°C, C12H14N2O4 (KBr) 3040, 1720; 2 (CDCl3) 7.60–7.95 (m, 4 H, aromatic), 4.70 (s, 2 H, methylene); 3 (CDCl3) 161 (M+–CO2).

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Table 1  Condensation of maleic and phthalic anhydrides with amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction time (t/min)</th>
<th>Solvent of crystallization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glycine</td>
<td>N-Carboxymethylmaleimide (4)</td>
<td>3</td>
<td>Water</td>
</tr>
<tr>
<td>2</td>
<td>Alanine</td>
<td>N-(α-Carboxylethyl)maleimide (5)</td>
<td>3</td>
<td>Water</td>
</tr>
<tr>
<td>3</td>
<td>2-Phenylglycine methyl ester</td>
<td>N-(α-Methoxycarbonylbenzyl)maleimide (6)</td>
<td>2</td>
<td>Methanol</td>
</tr>
<tr>
<td>4</td>
<td>Benzylamine</td>
<td>N-Benzylmaleimide (7)</td>
<td>2</td>
<td>Chloroform</td>
</tr>
<tr>
<td>5</td>
<td>Allylamine</td>
<td>N-Allylmaleimide (8)</td>
<td>2</td>
<td>Methanol</td>
</tr>
<tr>
<td>6</td>
<td>Benzylamine</td>
<td>N-Benzylphthalimide (9)</td>
<td>3</td>
<td>Water</td>
</tr>
<tr>
<td>7</td>
<td>Glycine</td>
<td>N-(Carboxymethyl)phthalimide (10)</td>
<td>3</td>
<td>Chloroform</td>
</tr>
</tbody>
</table>

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References