Microwave-induced One-pot Synthesis of *N*-carboxyalkyl Maleimides and Phthalimides†

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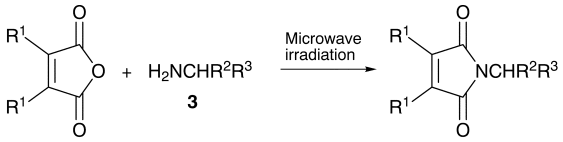
Maleic and phthalic anhydride condenses with amino acids and alkylamines under microwave irradiation to afford N-substituted maleimides and phthalimides in excellent yields.

Maleimides constitute an important class of chemically and biologically significant compounds.[1] Reagents containing a maleimido ligand tethered to an active ester group are in high demand in modern chemistry and biotechnology.[2] In addition, *N*-alkylphthalimides have received renewed interest as a source of functionalized β-lactams.[3] 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 Mitsunobo reaction conditions.[4] Maleimide-linked esters are prepared by cyclo-condensation of maleimino acids in the presence of acetic anhydride and sodium acetate or from *N*-(ethoxy-carbonyl)maleimide and amino acids.[5] However, these methods have limitations of general applicability owing to low yield, extensive by-product formation and harsh reaction conditions.[6]

There has been a growing interest in the use of microwave irradiation for heating in organic synthesis.[7] 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.[8] Recently microwave irradiation has been utilized for N-alkylation of phthalimide in dry media under phase-transfer catalysis.[9] Although the synthesis of N-arylmaleimides proceeds in excellent yields, the synthesis of N-alkylmaleimides under identical conditions is less satisfactory.[10] 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.



1 $R^1 = H$
2 $R^1R^1 = C_4H_4$

4 $R^1 = R^2 = H$, $R^3 = CO_2H$
5 $R^1 = H$, $R^2 = Me$, $R^3 = CO_2H$
6 $R^1 = H$, $R^2 = Ph$, $R^3 = CO_2Me$
7 $R^1 = R^2 = H$, $R^3 = Ph$
8 $R^1 = R^2 = H$, $R^3 = C_3H_5$
9 $R^1R^1 = C_4H_4$, $R^2 = H$, $R^3 = Ph$
10 $R^1R^1 = C_4H_4$, $R^2 = H$, $R^3 = CO_2H$

Equimolecular amounts of maleic anhydride (**1**) and amino acid (**3**, $R^2 = H$, Me, Ph; $R^3 = CO_2H$, CO_2Me) were placed in an open Erlenmeyer flask and heated in a domestic microwave oven for an appropiate 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**, $R^2 = H$, $R^3 = Ph$) and amino acids (**3**, $R^2 = H$, $R^3 = CO_2H$) affording N-substituted phthalimides (**9** and **10**, respectively) in 89–95% yields. Interestingly, our procedure of microwave heating excludes polymerization.[6] Further, alkylamines (**3**, $R^2 = H$, $R^3 = Ph$, vinyl) efficiently undergo one-pot condensation with **1** 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*-alkyl-maleimides 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 infrared spectrometer in KBr discs. The ^1H NMR spectra were recorded on Varian T-60 and JEOL JNM FX90Q spectrometers using Me_4Si 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**, $R^2 = H$, $R^3 = CO_2H$, 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 wshed with cold water (2 × 10 ml), dried (Na_2SO_4), filtered and the solvent removed.

N-*Carboxymethylmaleimide* **4**: yield 94%, mp 112–13 °C; ν_{max}/cm^{-1} (KBr) 3050, 1710; δ_H ($CDCl_3$) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, methylene); *m*/*z* 111 ($M^+ - CO_2$) (Found: 46.5; H, 3.15; N, 9.1. $C_6H_5NO_4$ requires C, 46.44; H, 3.25; N, 9.01%).

N-(α-*Carboxyethyl*)*maleimide* **5**: yield 90%, mp 97–98 °C; ν_{max}/cm^{-1} (KBr) 3060, 1710; δ_H (CD_3COCD_3) 6.85 (s, 2 H, olefinic), 3.80 (q, 1 H, methine), 2.1 (d, 3 H, methyl); *m*/*z* 125 ($M^+ - CO_2$) (Found: C, 49.8; H, 4.2; N, 8.2. $C_7H_7NO_4$ requires C, 49.69; H, 4.17; N, 8.25%).

N-(α-*Methoxycarbonylbenzyl*)*maleimide* **6**: yield 95%, mp 87–89 °C (lit.[4(c)], 88 °C); ν_{max}/cm^{-1} (KBr) 3010, 1725, 1710; δ_H ($CDCl_3$) 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); *m*/*z* 221 (M^+).

N-*Benzylmaleimide* **7**: yield 96%, mp 69–70 °C (lit.,[4(c)] 69.5–70.5 °C); ν_{max}/cm^{-1} (KBr) 3050, 1705; δ_H ($CDCl_3$) 7.20–7.40 (m, 5 H, aromatic), 6.70 (s, 2 H, olefinic) 4.68 (s, 2 H, methylene); *m*/*z* 237 (M^+).

N-*Allylmaleimide* **8**: yield 82%, mp 42–43 °C (lit.,[4(c)] 42.5–43 °C); ν_{max}/cm^{-1} (KBr) 3000, 1710; δ_H($CDCl_3$) 6.72 (s, 2 H, olefinic), 5.80 (m, 1 H, vinylc), 5.12–5.24 (m, 2 H, vinylic), 4.10 (dt, 2 H, *J* 5.6 Hz, vinylic); *m*/*z* 137 (M^+).

N-*Benzylphthalimide* **9**: yield 89%, mp 119–20 °C (lit.,[4(c)] 118.5–119.5 °C); ν_{max}/cm^{-1} (KBr) 3060, 1700; δ_H ($CDCl_3$) 7.65–7.88 (m, 4 H, aromatic), 7.20–7.45 (m, 5 H, aromatic), 4.80 (s, 2 H, olefinic); *m*/*z* 237 (M^+).

N-*Carboxymethylphthalimide* **10**: yield 95%, mp 110–11 °C; ν_{max}/cm^{-1} (KBr) 3040, 1720; δ_H (CD_3COCD_3) 7.60–7.95 (m, 4 H, aromatic), 4.70 (s, 2 H, methylene); *m*/*z* 161 (M^+–CO_2). (Found: C, 58.6, H, 3.3, N, 6.9. $C_{10}H_7NO_4$ requires C, 58.52, H, 3.44, N, 6.83%).

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Condensation of maleic and phthalic anhydrides with amines

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

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