

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

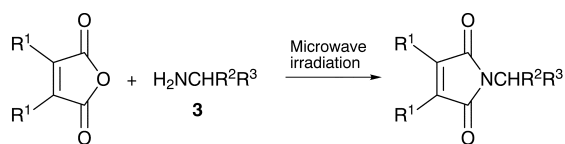
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Maleic and phthalic anhydride condenses with amino acids and alkylamines under microwave irradiation to afford *N*-substituted maleimides and phthalimides in excellent yields.

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

There has been a growing interest in the use of microwave irradiation for heating in organic synthesis.<sup>7</sup> 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.<sup>8</sup> Recently microwave irradiation has been utilized for *N*-alkylation of phthalimide in dry media under phase-transfer catalysis.<sup>9</sup> Although the synthesis of *N*-arylmaleimides proceeds in excellent yields, the synthesis of *N*-alkylmaleimides under identical conditions is less satisfactory.<sup>10</sup> 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<sup>1</sup> = H  
2 R<sup>1</sup>R<sup>1</sup> = C<sub>4</sub>H<sub>4</sub>

4 R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = CO<sub>2</sub>H  
5 R<sup>1</sup> = H, R<sup>2</sup> = Me, R<sup>3</sup> = CO<sub>2</sub>H  
6 R<sup>1</sup> = H, R<sup>2</sup> = Ph, R<sup>3</sup> = CO<sub>2</sub>Me  
7 R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = Ph  
8 R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = C<sub>3</sub>H<sub>5</sub>  
9 R<sup>1</sup>R<sup>1</sup> = C<sub>4</sub>H<sub>4</sub>, R<sup>2</sup> = H, R<sup>3</sup> = Ph  
10 R<sup>1</sup>R<sup>1</sup> = C<sub>4</sub>H<sub>4</sub>, R<sup>2</sup> = H, R<sup>3</sup> = CO<sub>2</sub>H

Equimolecular amounts of maleic anhydride (**1**) and amino acid (**3**, R<sup>2</sup> = H, Me, Ph; R<sup>3</sup> = CO<sub>2</sub>H, CO<sub>2</sub>Me) 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**, R<sup>2</sup> = H, R<sup>3</sup> = Ph) and amino acids (**3**, R<sup>2</sup> = H, R<sup>3</sup> = CO<sub>2</sub>H) affording *N*-substituted phthalimides (**9** and **10**, respectively) in 89–95% yields. Interestingly, our procedure of microwave heating excludes polymerization.<sup>6</sup> Further, alkylamines (**3**, R<sup>2</sup> = H, R<sup>3</sup> = 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*-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 infrared spectrometer in KBr discs. The <sup>1</sup>H NMR spectra were recorded on Varian T-60 and JEOL JNM FX90Q spectrometers using Me<sub>4</sub>Si as internal standard ( $\delta$ /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<sup>2</sup> = H, R<sup>3</sup> = CO<sub>2</sub>H, 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 (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed.

***N*-Carboxymethylmaleimide 4:** yield 94%, mp 112–13 °C;  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3050, 1710;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 6.70 (s, 2 H, olefinic), 3.75 (s, 2 H, methylene);  $m/z$  111 (M<sup>+</sup> – CO<sub>2</sub>) (Found: 46.5; H, 3.15; N, 9.1. C<sub>6</sub>H<sub>7</sub>NO<sub>4</sub> requires C, 46.44; H, 3.25; N, 9.01%).

***N*-( $\alpha$ -Carboxyethyl)maleimide 5:** yield 90%, mp 97–98 °C;  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3060, 1710;  $\delta_{\text{H}}$  (CD<sub>3</sub>COCD<sub>3</sub>) 6.85 (s, 2 H, olefinic), 3.80 (q, 1 H, methine), 2.1 (d, 3 H, methyl);  $m/z$  125 (M<sup>+</sup> – CO<sub>2</sub>) (Found: C, 49.8; H, 4.2; N, 8.2. C<sub>7</sub>H<sub>7</sub>NO<sub>4</sub> requires C, 49.69; H, 4.17; N, 8.25%).

***N*-( $\alpha$ -Methoxycarbonylbenzyl)maleimide 6:** yield 95%, mp 87–89 °C (lit.<sup>4(c)</sup>, 88 °C);  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3010, 1725, 1710;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 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<sup>+</sup>).

***N*-Benzylmaleimide 7:** yield 96%, mp 69–70 °C (lit.<sup>4(c)</sup>, 69.5–70.5 °C);  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3050, 1705;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.20–7.40 (m, 5 H, aromatic), 6.70 (s, 2 H, olefinic) 4.68 (s, 2 H, methylene);  $m/z$  237 (M<sup>+</sup>).

***N*-Allylmaleimide 8:** yield 82%, mp 42–43 °C (lit.<sup>4(c)</sup>, 42.5–43 °C);  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3000, 1710;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 6.72 (s, 2 H, olefinic), 5.80 (m, 1 H, vinylic), 5.12–5.24 (m, 2 H, vinylic), 4.10 (dt, 2 H, *J* 5.6 Hz, vinylic);  $m/z$  137 (M<sup>+</sup>).

***N*-Benzylphthalimide 9:** yield 89%, mp 119–20 °C (lit.<sup>4(c)</sup>, 118.5–119.5 °C);  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3060, 1700;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 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<sup>+</sup>).

***N*-Carboxymethylphthalimide 10:** yield 95%, mp 110–11 °C;  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3040, 1720;  $\delta_{\text{H}}$  (CD<sub>3</sub>COCD<sub>3</sub>) 7.60–7.95 (m, 4 H, aromatic), 4.70 (s, 2 H, methylene);  $m/z$  161 (M<sup>+</sup> – CO<sub>2</sub>). (Found: C, 58.6; H, 3.3; N, 6.9. C<sub>10</sub>H<sub>7</sub>NO<sub>4</sub> 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	<i>N</i> -Carboxymethylmaleimide ( <b>4</b> )	3	Water
2	Alanine	<i>N</i> -( $\alpha$ -Carboxyethyl)maleimide ( <b>5</b> )	3	Water
3	2-Phenylglycine methyl ester	<i>N</i> -( $\alpha$ -Methoxycarbonylbenzyl)maleimide ( <b>6</b> )	2	Methanol
4	Benzylamine	<i>N</i> -Benzylmaleimide ( <b>7</b> )	2	Chloroform
5	Allylamine	<i>N</i> -Allylmaleimide ( <b>8</b> )	2	Methanol
6	Benzylamine	<i>N</i> -Benzylphthalimide ( <b>9</b> )	3	Water
7	Glycine	<i>N</i> -(Carboxymethyl)phthalimide ( <b>10</b> )	3	Chloroform

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## References

- 1 J. E. T. Corrie, *J. Chem. Soc., Perkin Trans 1*, 1994, 2975.
- 2 T. Kitagawa, T. Kawasaki and H. Munechika, *J. Biochem.*, 1982, **92**, 585.
- 3 D. D. Pietro, R. M. Borzilleri and S. M. Weinreb, *J. Org. Chem.*, 1994, **59**, 5856.
- 4 (a) G. B. Gill, G. B. James, K. V. Oates and G. J. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2567; (b) M. A. Walker, *J. Org. Chem.*, 1995, **60**, 5352; (c) P. Y. Reddy, S. Kondo, T. Toru and Y. Ueno, *J. Org. Chem.*, 1997, **62**, 2652.
- 5 O. Nielsen and O. Buchardt, *Synthesis*, 1991, 819 and references cited therein.
- 6 M. P. Stevens, *J. Polym. Sci. Polym. Lett. Ed.*, 1984, **22**, 467.
- 7 (a) R. Laurent, A. Leporterie, J. Dubac, J. Berlan, S. Lauverie and F. M. Audhuy, *J. Org. Chem.*, 1992, **57**, 7099 and references cited therein; (b) S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
- 8 (a) G. Bram, A. Loupy and D. Villemerin, in *Solid Supports and Catalysts in Organic Chemistry*, Ellis Horwood, London, 1992; (b) A. Boruah, M. Baruah, D. Prajapati and J. S. Sandhu, *Chem. Lett.*, 1996, 965.
- 9 D. Bogda and J. Pielichowski, *Synlett*, 1996, 873.
- 10 (a) N. B. Metha, A. P. Phillips, F. F. Lui and R. E. Brooks, *J. Org. Chem.*, 1960, **25**, 1012; (b) D. H. Rich, P. D. Gesellchen, D. Paul, A. Tong, T. A. Cheung and C. K. Buckner, *J. Med. Chem.*, 1975, **18**, 1004.