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## A NEW AND RAPID *N*-ALKYLATION OF 3,6-EPOXY- HEXAHYDROPHthalIMIDES

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### ABSTRACT

Rapid *N*-alkylation of 3,6-epoxyhexahydrophthalimides with a series of halides were performed under solvent-free conditions coupled with microwave irradiation. The isolated yield of *N*-substituted 3,6-epoxyhexahydrophthalimides varied from 82 to 98%.

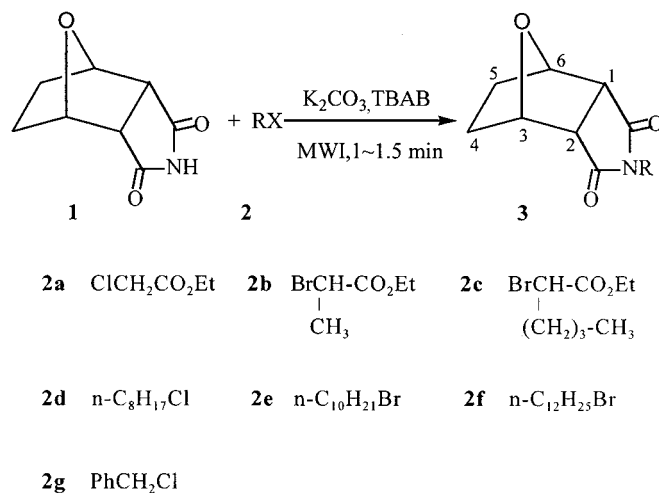
Cantharidin and norcantharidin (3,6-epoxyhexahydrophthalimide) possess antitumor activity and were used as antitumor drug to cure liver cancer.<sup>1–3</sup> *N*-substituted 3,6-epoxyhexahydrophthalimides have been shown to possess anticonvulsant, hypotensive, anthelmintic and antitumour activity, some of them can be used as insecticide and germicide.<sup>4–8</sup>

Microwave organic reaction enhancement chemistry (MOREC) is a new subject developed in recent years,<sup>9</sup> various organic reactions have been investigated<sup>10,11</sup> and several papers on its use in alkylations were reported lately.<sup>12–14</sup> Here we would like to describe a new and rapid synthesis of

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*N*-alkyl-3,6-epoxyhexahydrophthalimides via alkylation of 3,6-epoxyhexahydrophthalimide in 'dry media' under microwave irradiation.



The alkylation of 3,6-epoxyhexahydrophthalimide was simply achieved by microwave irradiation of the mixture of 3,6-epoxyhexahydrophthalimides (**1**), alkyl halides (**2**), potassium carbonate and a catalytic amount of tetrabutylammonium bromide (TBAB), followed by extraction and purification to give the products in 82–98% yield (Tables 1 and 2).

**Table 1.** *N*-Alkylation of 3,6-Epoxyhexahydrophthalimide

Entry	<b>2/1</b> (mol)	Irradiation Time (min)	Irradiation Power (W)	Yield (%)	M.P. (°C)
<b>3a</b>	1.25 : 1	1.0	240	95	101–102
<b>3b</b>	1.1 : 1	1.5	240	92	94–95
<b>3c</b>	1.1 : 1	1.5	240	98	
<b>3d</b>	1.1 : 1	1.5	400	82	
<b>3e</b>	1.1 : 1	1.5	400	90	
<b>3f</b>	1.1 : 1	1.5	400	98	
<b>3g</b>	1.1 : 1	1.5	400 <sup>15</sup>	94	116–119



Table 2. Analytical Data of Products 3

Entry	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ, CDCl <sub>3</sub> )	Elementary Analyses (Calc., %)		
			C	H	N
<b>3a</b>	3472, 1770,	4.9 (m, 2H, 3,6-H)	56.71	6.05	5.40
	1743, 1714,	4.1–4.3 (q, 2H, -O-CH <sub>2</sub> -)	(56.91)	(5.97)	(5.53)
	1222, 1187	4.2 (s, 2H, -N-CH <sub>2</sub> )			
		3.0 (s, 2H, 1,2-H)			
		2.0–1.4 (m, 4H, 4,5-H)			
		1.3 (t, 3H, -CH <sub>3</sub> )			
<b>3b</b>	3465, 1778,	4.9 (m, 2H, 3,6-H)	58.20	6.53	5.10
	1735, 1707,	4.7 (q, 1H, -N-CHCH <sub>3</sub> )	(58.42)	(6.41)	(5.24)
	1250, 1201	4.2 (m, 2H, -OCH <sub>2</sub> -)			
		2.9 (s, 2H, 1,2-H)			
		2.1–1.6 (m, 4H, 4,5-H)			
		1.5 (d, 3H, NCH-CH <sub>3</sub> )			
<b>3c</b>	3465, 1778,	4.9 (m, 2H, 3,6-H)	62.35	7.40	4.40
	1743, 1707,	4.6 (t, 1H, -N-CHCH <sub>2</sub> -)	(62.12)	(7.49)	(4.53)
	1250, 1187	4.2 (m, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )			
		2.9 (s, 2H, 1,2-H)			
		2.4–2.0, 1.0–1.6			
		(m, 6H, (CH <sub>2</sub> ) <sub>3</sub> )			
<b>3d</b>	3460, 1771,	4.8 (m, 2H, 3,6-H)	68.53	9.23	4.89
	1701, 1187	3.4 (t, 2H, -N-CH <sub>2</sub> )	(68.79)	(9.02)	(5.01)
		2.9 (s, 2H, 1,2-H)			
		2.0–1.5 (m, 4H, 4,5-H)			
		1.4–0.6 (m, 15H,			
		N-C-(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub> )			
<b>3e</b>	3458, 1770,	4.9 (m, 2H, 3,6-H)	70.58	9.26	4.79
	1700, 1187	3.4 (t, 2H, -N-CH <sub>2</sub> -)	(70.32)	(9.51)	(4.56)
		2.9 (s, 2H, 1,2-H)			
		2.0–1.6 (m, 4H, 4,5-H)			
		1.6–0.6 (m, 19H,			
		-N-C-(CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub> )			

(continued)



**Table 2.** Continued

Entry	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR (δ, CDCl <sub>3</sub> )	Elementary Analyses (Calc., %)		
			C	H	N
<b>3f</b>	3458, 1771,	4.9 (m, 2H, 3,6-H)	71.85	9.92	4.02
	1700, 1187	3.4 (t, 2H, -N-CH <sub>2</sub> )	(71.60)	(9.91)	(4.18)
		2.9 (s, 2H, 1,2-H)			
		2.0–1.6 (m, 4H, 4,5-H)			
		1.6–0.6 (m, 23H, -N-C-(CH <sub>2</sub> ) <sub>10</sub> CH <sub>3</sub> )			
<b>3g</b>	3444, 3064,	7.3 (s, 5H, Ar-H)	69.83	5.99	5.35
	3029, 1771,	4.9 (m, 2H, 3,6-H)	(70.02)	(5.88)	(5.44)
	1693, 1180	4.6 (s, 2H, -N-CH <sub>2</sub> -Ph)			
		2.9 (s, 2H, 1,2-H)			
		2.0–1.4 (m, 4H, 4,5-H)			

## EXPERIMENTAL

### General Considerations

IR spectra were recorded on a Nicolet 5DXB-FT infrared spectrometer, <sup>1</sup>H NMR spectra were recorded on a JEOL FX-90Q spectrometer using TMS as internal standard. Microanalyses were carried out by Perkin-Elmer 2400 CHN elemental analysis instrument. Norcantharidin and norcantharidinimide were synthesized according to the Refs 16 and 17.

### General Procedure for the Alkylation of 3,6-Epoxyhexahydrophthalimides

A mixture of 3,6-epoxyhexahydrophthalimides (**1**, 0.48 g, 7.9 mmol), ethyl chloroacetate (**2a**, 1.21 g, 9.88 mmol), TBAB (0.05 g, 0.16 mmol) and potassium carbonate (1.5 g, 11 mmol) were irradiated in a Galanz WP800BS domestic oven in an open container for 1 min at 240 W. The cooled mixture was extracted with 50 mL methylene chloride, then the solvent was removed *in vacuo* and the residue purified by preparative thin layer chromatography (silica gel: 100–200 mesh, eluent: ethyl acetate/cyclohexane = 1/1, v/v, *R*<sub>f</sub> = 0.47) to give **3a**, the yield was 95%.



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- If  $Al_2O_3$  was used as external bath and the microwave power and microwave irradiation time were 560 W and 1.0 min respectively, the yield was 64%, but the product was *N*-benzylphthalimide instead of **3g**. This was confirmed by TLC, IR,  $^1H$ NMR and elemental analysis.  $^1H$ NMR ( $CHCl_3$ ) 8.0–7.6 (m, 5H,  $C_6H_5$ ), 7.6–7.1 (m, 4H,  $C_6H_4$ ), 4.84 (s, 2H,  $CH_2$ ). Anal. calcd. for  $C_{15}H_{11}NO_2$ : C, 75.95; H, 4.64; N, 5.91. Found: C, 75.99; H, 4.81; N, 6.16. Because the bath allows a fast heating and a much high temperature of the reaction mixture, *N*-benzylphthalimide was produced via the degradation of *N*-benzyl-norcantharidinimide. See: Bram, G.; Loupy, A.; Majdoub, M. *Tetrahedron* **1990**, 46, 5167 and Reinhoudt, D.N.; et al. *Tetrahedron* **1974**, 30, 2093, 4777.
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