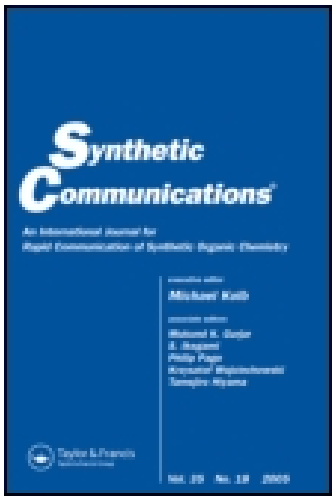

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A NEW AND RAPID N-ALKYLATION OF 3,6-EPOXY-HEXAHYDROPHTHALIMIDES

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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.[1–3] *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.[4–8]

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

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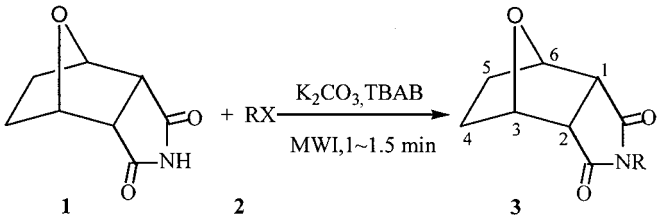
N-alkyl-3,6-epoxyhexahydrophthalimides via alkylation of 3,6-epoxyhexahydrophthalimide in 'dry media' under microwave irradiation.



1 **2** **3**

2a $ClCH_2CO_2Et$ **2b** $BrCH(CH_3)CO_2Et$ **2c** $BrCH((CH_2)_3CH_3)CO_2Et$

2d $n\text{-}C_8H_{17}Cl$ **2e** $n\text{-}C_{10}H_{21}Br$ **2f** $n\text{-}C_{12}H_{25}Br$

2g $PhCH_2Cl$

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

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Table 2. Analytical Data of Products **3**

Entry	IR (cm^{-1})	^{1}H NMR (δ, $CDCl_3$)	Elementary Analyses (Calc., %) C	H	N
3a	3472, 1770, 1743, 1714, 1222, 1187	4.9 (m, 2H, 3,6-H) 4.1–4.3 (q, 2H, -O-CH_2-) 4.2 (s, 2H, -N-CH_2) 3.0 (s, 2H, 1,2-H) 2.0–1.4 (m, 4H, 4,5-H) 1.3 (t, 3H, -CH_3)	56.71 (56.91)	6.05 (5.97)	5.40 (5.53)
3b	3465, 1778, 1735, 1707, 1250, 1201	4.9 (m, 2H, 3,6-H) 4.7 (q, 1H, -N-$CHCH_3$) 4.2 (m, 2H, -OCH_2-) 2.9 (s, 2H, 1,2-H) 2.1–1.6 (m, 4H, 4,5-H) 1.5 (d, 3H, NCH-CH_3) 1.2 (t, 3H, -CH_2CH_3)	58.20 (58.42)	6.53 (6.41)	5.10 (5.24)
3c	3465, 1778, 1743, 1707, 1250, 1187	4.9 (m, 2H, 3,6-H) 4.6 (t, 1H, -N-$CHCH_2$-) 4.2 (m, 2H, -OCH_2CH_3) 2.9 (s, 2H, 1,2-H) 2.4–2.0, 1.0–1.6 (m, 6H, $(CH_2)_3$) 2.0–1.6 (m, 4H, 4,5-H) 1.2 (t, 3H, -OCH_2CH_3) 0.9 (t, 3H, -CH_2CH_3)	62.35 (62.12)	7.40 (7.49)	4.40 (4.53)
3d	3460, 1771, 1701, 1187	4.8 (m, 2H, 3,6-H) 3.4 (t, 2H, -N-CH_2) 2.9 (s, 2H, 1,2-H) 2.0–1.5 (m, 4H, 4,5-H) 1.4–0.6 (m, 15H, N-C-$(CH_2)_6CH_3$)	68.53 (68.79)	9.23 (9.02)	4.89 (5.01)
3e	3458, 1770, 1700, 1187	4.9 (m, 2H, 3,6-H) 3.4 (t, 2H, -N-CH_2-) 2.9 (s, 2H, 1,2-H) 2.0–1.6 (m, 4H, 4,5-H) 1.6–0.6 (m, 19H, -N-C-$(CH_2)_8CH_3$)	70.58 (70.32)	9.26 (9.51)	4.79 (4.56)

(*continued*)

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Table 2. Continued

Entry	IR (cm^{-1})	^1H NMR (δ, $CDCl_3$)	Elementary Analyses (Calc., %)		
			C	H	N
3f	3458, 1771, 1700, 1187	4.9 (m, 2H, 3,6-H) 3.4 (t, 2H, -N-CH_2) 2.9 (s, 2H, 1,2-H) 2.0–1.6 (m, 4H, 4,5-H) 1.6–0.6 (m, 23H, -N-C-$(CH_2)_{10}CH_3$)	71.85 (71.60)	9.92 (9.91)	4.02 (4.18)
3g	3444, 3064, 3029, 1771, 1693, 1180	7.3 (s, 5H, Ar-H) 4.9 (m, 2H, 3,6-H) 4.6 (s, 2H, -N-CH_2-Ph) 2.9 (s, 2H, 1,2-H) 2.0–1.4 (m, 4H, 4,5-H)	69.83 (70.02)	5.99 (5.88)	5.35 (5.44)

EXPERIMENTAL

General Considerations

IR spectra were recorded on a Nicolet 5DXB-FT infrared spectrometer, ^1H 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 norcanthanridinimide 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, $R_f = 0.47$) to give **3a**, the yield was 95%.

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15. 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, ^{1}H NMR and elemental analysis. ^{1}H 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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