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Synthesis of Furonaphthalimides with Potential Photosensitizing Biological Activity

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ABSTRACT

A series of naphthalimides has been synthesized; 2,6-dimethyl-2,3H-furo[2,3-b][1]naphtho[4a,7a—e,f]pyrida-5,7-dione was obtained in a one-pot synthesis through the rearrangement and acidification of N-methyl-4-allyloxy-1,8-naphthalimide. The absoption and fluorescence of these furonaphthalimides and their precursors were recorded.

1 INTRODUCTION

1,8-Naphthalimide type dyes usually have very strong fluorescence,[1–3] and for this reason can be used as fluorescence probes, e.g. for hypoxic cells in solid tumors,[4,5] as solar energy collectors, as electroptically sensitive materials,[6,7] and for laser activity.[8,9] We have previously reported the synthesis and photooxygenation of some trimethylfuronaphthalimides as potential probes for singlet oxygen;[10] we have also studied their properties as DNA intercalator.[11] It is known that furocoumarin type dyes show very strong photobiological activity as the consequence of their intercalation between the base pairs of DNA in the dark, and their photocycloaddition with pyrimidine bases, particularly thymine. In order to prevent the occurrence of interstrand crosslinkage with DNA (through photoactive α-pyrone and furan sites) efforts have been made to develop new dyes which only permit monofunctional photobinding with DNA. We report here the synthesis and spectra of some dimethylfuronaphthalimides, which were designed as new potential DNA intercalators, with a photo-inactive pyridine site, instead of a photoactive pyrone site.

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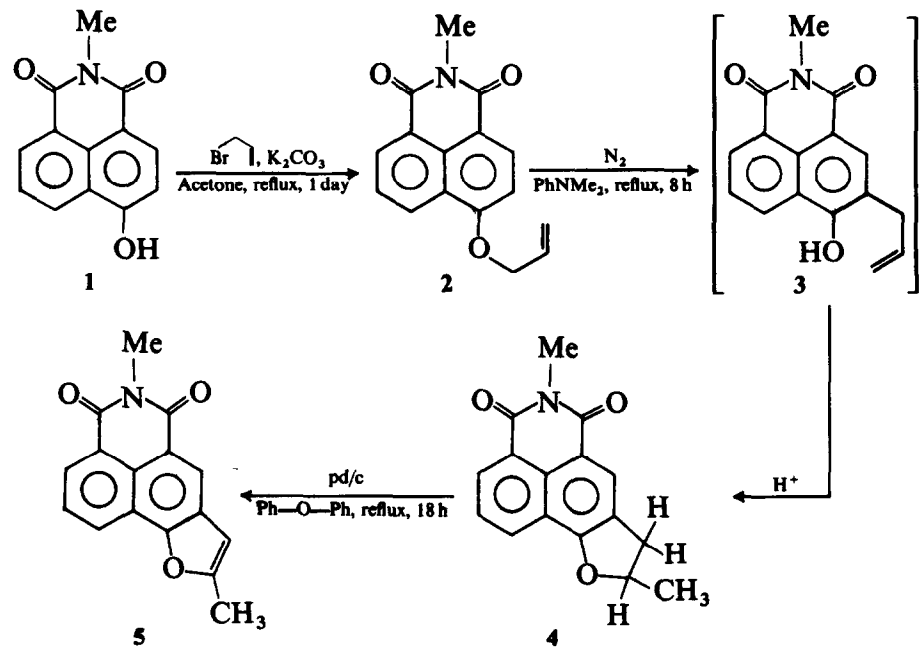
2 RESULTS AND DISCUSSION

The route used for compound **5** was as shown in the scheme below. Starting materials were prepared as reported previously.[10]



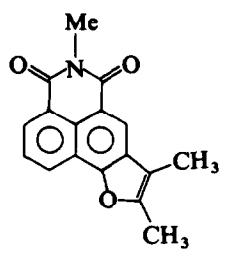
Compound **2** was obtained in 76% yield through the condensation of compound **1** with allyl bromide; the IR spectrum confirmed the absence of an OH group and the ^{1}H NMR spectrum showed peaks at δ = 1·63(d), 3·68 and 5·42(m), corresponding to the allyl group. The formation of compound **3** through Claisen rearrangement of compound **2** was anticipated, but during the rearrangement of compound **2** by refluxing in *N*,*N*-dimethylaniline for 8 h and acidificiation with hydrochloric acid, no formation of compound **3** was observed, only compound **4** being formed in 50% yield. This research is thus different from that expected from previous investigations of similar reactions.[12–14] It is suggested that compound **3** is a reactive species and is readily cyclized to compound **4** in the acidic reaction condition used, without further treatment in concentrated sulphuric acid. The use of a nitrogen atmosphere in the reaction is very important and prevents the formation of tars due to the oxidation reactions.

In the dehydration of **4** and **5** fresh Pd/C catalyst is necessary to ensure satisfactory reaction.

The UV-absorption and fluorescence maxima of compound **5** were at shorter wavelengths than those of compound **6** containing two methyl groups on the furan ring, and at even shorter wavelength than the uncyclized precursor **4**.

TABLE 1
The UV and FL Spectra Data of Furonaphthalimides and their Precursors

Compound no.	*UV* $\lambda_{max}(log\ \varepsilon)$	*FL* $\lambda_{max}(\phi)$	*Reference*
1	382·4 (4·0374)	446·1 (0·05)	
2	364·0 (4·1173)	439·6 (0·11)	
4	389·6 (4·0374)	471·0 (0·17)	
5	371·8 (3·7427)	446·2 (0·11)	
6	390·0 (4·2083)	471·8 (0·10)	10
7	361·2 (4·3410)	445·2 (0·99)	10
8	362·0 (4·1499)	443·5 (0·81)	10



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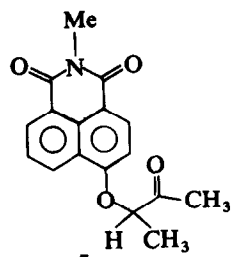

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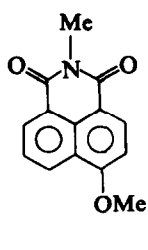

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3 EXPERIMENTAL

3.1 General

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were recorded on a Nicolet FTIR-20sx, mass spectra on a Hitachi M80, ^{1}H-NMR on a Bruker Wp-100sy (100 MHz) using $CDCl_3$ or TMS as internal standard. Combustion analysis for elemental composition was carried out on an Italy MOD.1106 analyzer run by the anlaysis centre of the East China University of Science and Technology. Absorption spectra were measured in absolute ethanol on a Shimadzu UV-265; fluroescence spectra were measured on a Perkin Elmer LS 50, with quinine sulphate in sulphuric acid as the quantum yield standard.

3.2 Synthesis of *N*-methyl-4-hydroxynaphthalimide(1)

A mixture of 4-bromo-1,8-naphthalic anhydride (10 g) and aqueous methylamine (150 ml) was stirred at 85°C for 2 h. The yellow precipitate was filtered after cooling, giving the yellow-coloured *N*-methyl-4-bromo-1,8-naphthalimide in 90% yield, m.p. 176–177°C.

A mixture of *N*-methyl-4-bromo-1,8-naphthalimides (4 g) CH_3ONa (7·0 g) and $CuSO_4$ (0·5 g) was refluxed in methanol for 12 h. The precipitate was filtered, washed with dilute hydrochloric acid and then with water, to give *N*-methyl-4-methoxy-1,8-naphthalimine, in 86% yield, m.p. 195–198°C. The hydrolysis of *N*-methyl-4-methoxy-1,8-naphthalimide to the corresponding 4-hydroxy compound was carried out according to our previous report.[7]

3.3 Synthesis of *N*-methyl-4-allyloxy-1,8-naphthalmide(2)

A mixture of *N*-methyl-4-hydroxy-1,8-naphthalimide(1) (5 g), allyl bromide (5 g), K_2CO_3 (4·5 g), and acetone (100 ml) was refluxed for 24 h; after removal of solvents, a solution of 5% NaOH was added and the resulting precipitate was filtered, washed, and dried to give *N*-methyl-4-allyloxy-1,8-naphthalimide(2) in 76% yield, m.p. 172–173°C (EtOH).

IR(KBr): 2900 cm^{-1}, 1680, 1660 (C=O), 1400 (*N*-CH_3), 1580, 1360, 1260, 1220, 1080, 1020, 780 cm^{-1}.

$C_{16}H_{13}NO_3$: Calcd, C, 71·89; H, 4·90; N, 5·24. Found, C, 72·03; H, 5·05; N, 5·14.

3.4 Synthesis of 2,6-dimethyl-2,3*H*-furo[2,3-*b*][1]naphtho[4*a*,7*a*–*e*, *f*]pyrida-5,7-dione (4)

A mixture of compound **2** (1·8 g) and *N*,*N*-dimethylaniline (18 ml) was refluxed for 8 h under a nitrogen atmosphere. After cooling, the reaction liquor was added to ice water and made alkaline with aqueous NaOH. After filtration, the filtrate was acidified with hydrochloric acid to give a yellow precipitate, which was filtered, washed with water and dried to give compound **4** in 50% yield, m.p. 168–169°C (ethanol).

IR(KBr): 2900, 1690 (C=O), 1650, 1460, 1400 (N—CH_3), 1360, 1280, 1100, 1030, 780 cm.

^{1}H-NMR (CD_3COCD_3): δ = 1·63 (d, J = 5·3 Hz, 3H, 2-CH_3), 3·49 (s, 3H, N—CH_3), 3·68 (d, J = 10·5 Hz, 2H, 3-CH_2—), 5·42 (m, 1H, 2-CH—), 7·68 (dd, J_{XA} = 6·0 Hz, J_{XB} = 5·0 Hz, 1H, 9-H), 8·42 (dd, J_{AX} = 6·0 Hz, J_{AB} = 1·1 Hz, 1H, 10-H), 8·45 (dd, J_{BX} = 5·0 Hz, J_{BA} = 1·1 Hz, 1H, 8-H), 8·57 (s, 1H, 4-H).

MS(70 eV): *m/e*(%) 267 (100)[M^+], 252 (25) [M—CH_3].

$C_{16}H_{13}NO_3$: Calcd, c, 71·89; H, 4·90; N, 5·24. Found, c, 71·71; H, 4·78; N, 4·94.

3.5 Synthesis of 2,6-dimethyl-furo[2,3-*b*][1]naphtho[4*a*,7*a*–*e*, *f*]pyrida-5,7-dione (5)

A mixture of compound **4** (0·5 g) and Pd/C catalyst (0·5 g) prepared in our laboratories[15] and diphenyl ether (7 ml) was refluxed for 18 h. After filtering and cooling, a yellow precipitate of compound **5** was obtained in 60% yield, m.p. 218·5–219·5°C.

IR(KBr): 2920, 1700 (C=O), 1660, 1460, 1390, 1360, 1290, 1110, 780 cm.

^{1}H-NMR ($CDCl_3$): δ = 2·66 (d, J = 0·8 Hz, 3H, 2-CH_3), 3·56 (s, 3H, N—CH_3), 6·69 (d, J = 0·8 Hz, 1H, 3-H), 7·78 (dd, J_{XA} = 9·4 Hz, J_{XB} = 7·8 Hz, 1H, 9-H), 8·5 (dd, J_{AX} = 9·4 Hz, J_{XB} = 1·2 Hz, 1H, 10-H), 8·59 (dd, J_{BX} = 7·8 Hz, J_{BA} = 1·2 Hz, 1H, 8-H), 8·75 (s, 1H, 4-H).

MS(70 eV): *m/e*(%) 266 (14·2)[M^+ +1], 265 (19·4)[M^+], 208 (11·9) [M^+ —$CONCH_3$], 165 (11·1) [M^+ —$C_4H_6NO_2$].

$C_{16}H_{11}NO_3$: Calcd, C, 72·44; H, 4·18; N, 5·28. Found, C, 72·38; H, 4·21; N, 5·29.

ACKNOWLEDGEMENT

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