Dyes and Pigments **8** (1987) 399–404

Synthesis of Naphthoxazole Derivatives by the Application of the Vilsmeier–Haack Reaction: Part I

M. R. Jayant and S. Seshadri*

Dyes Research Laboratory, Department of Chemical Technology,
University of Bombay, Matunga, Bombay 400 019, India

(Received 17 November 1986; accepted 21 January 1987)

SUMMARY

The Vilsmeier–Haack reaction has been utilised for the synthesis of 5-nitro-2-naphth[2,1-d]oxazolylmalondialdehydes. The malondialdehydes were converted to the 2-pyrazolyl and the 2-pyrimidyl derivatives and thence to the corresponding 2-hetaryl 5-nitronaphth[2,1-d]oxazoles. 5-Acetamido derivatives of the latter were prepared and absorption and emission properties of the various compounds studied.

1 INTRODUCTION

We have previously reported[1] the synthesis of 2-hetaryl benzoxazoles and naphthoxazoles by use of the Vilsmeier-Haack reaction. Fluorescence characteristics of these derivatives were generally unsatisfactory. We were therefore interested in studying the possibilities of enhancing the fluorescence intensities of the naphthoxazole derivatives by suitable modifications in the naphthalene ring and we report here the synthesis of some 2-hetaryl naphth[2,1-*d*]oxazoles with different substituents in the naphthalene moiety.

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* To whom all correspondence should be addressed.

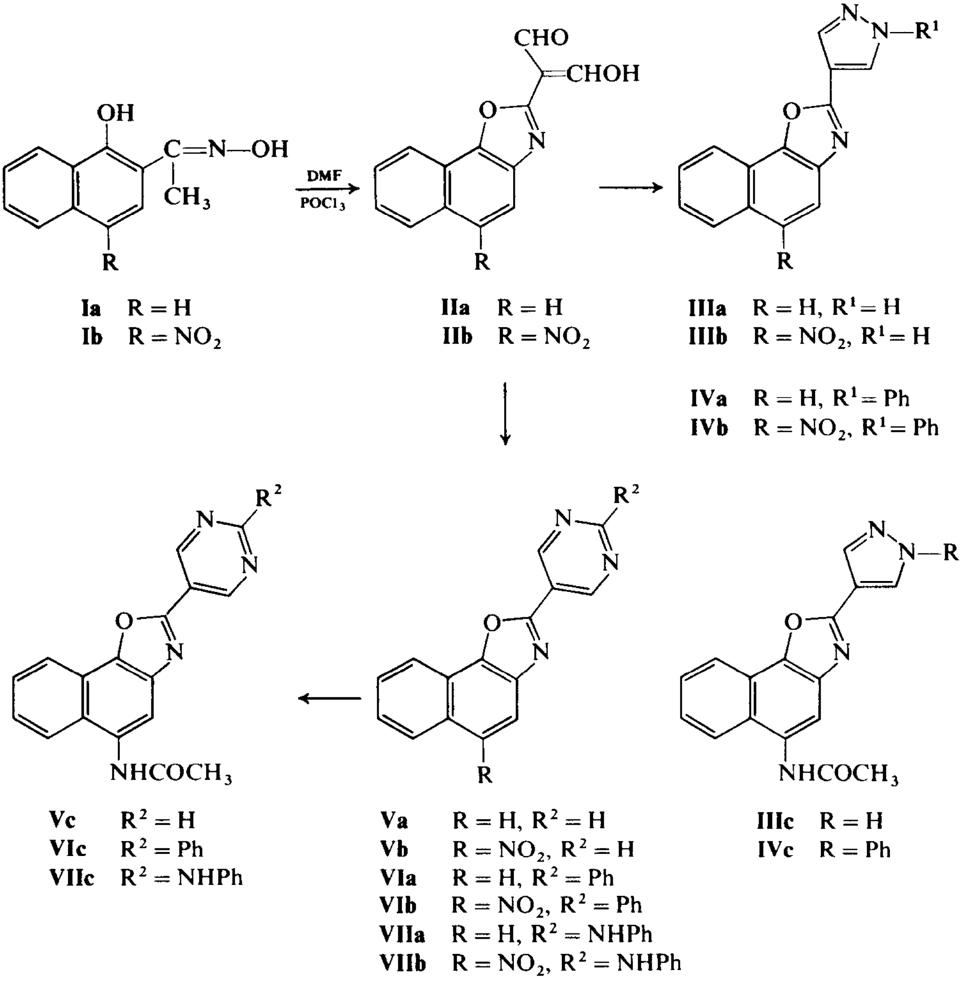
Dyes and Pigments 0143-7208/87/$03·50

2 RESULTS

Scheme 1 outlines the general routes adopted in the syntheses.

Beckmann rearrangement and Vilsmeier reaction on the oxime of 2-acetyl-1-hydroxy-4-nitronaphthalene (**Ib**) gave the 5-nitronaphth[2,1-*d*]oxazolylmalondialdehyde (**IIb**). The malondialdehydes were converted to a range of heterocyclic analogues by standard reactions.

The nitro-substituted 2-hetaryl naphthoxazoles were reductively acetylated to the corresponding acetamido compounds with the hope of improving fluorescence. However, the acetamido compounds did not exhibit satisfactory fluorescence and rather surprisingly in some cases the nitro



Ia R = H
Ib R = NO_2

IIa R = H
IIb R = NO_2

IIIa R = H, R^1 = H
IIIb R = NO_2, R^1 = H

IVa R = H, R^1 = Ph
IVb R = NO_2, R^1 = Ph

Vc R^2 = H
VIc R^2 = Ph
VIIc R^2 = NHPh

Va R = H, R^2 = H
Vb R = NO_2, R^2 = H
VIa R = H, R^2 = Ph
VIb R = NO_2, R^2 = Ph
VIIa R = H, R^2 = NHPh
VIIb R = NO_2, R^2 = NHPh

IIIc R = H
IVc R = Ph

Scheme 1

TABLE 1
Absorption and Emission Data[a]

Compound	λ^{abs}_{max} (*nm*)	(ε)	λ^{Exc} (*nm*)	λ^{Emi}_{max} (*nm*)	I_{max}	*Q* (*mg*)
Va	338·5	(3·97)	350	440	81	1·302
	311·5	(3·98)	—	—	—	—
Vb	344·5	(4·21)	380	450	48	6·770
	309·5	(4·28)	—	—	—	—
Vc	350·0	(4·43)	366	465	43	3·800
VIa	354·0	(4·53)	374	448	98	1·347
VIb	306·0	(4·02)	380	455	60	5·000
VIc	288·0	(4·39)	370	440	87	2·304
	350·0	(4·29)	—	—	—	—
VIIa	352·5	(4·40)	300	415	87	4·696
VIIb	350·0	(4·28)	390	455	27·5	2·032
VIIc	350·0	(4·43)	366	465	43	3·800

[a] λ^{abs}_{max}, Wavelength of maximum absorption; ε, extinction coefficient; λ^{Emi}_{max}, wavelength of maximum emission; λ^{Exc}, excitation wavelength; I_{max}, maximum intensity of emission; *Q*, weight of compound in 100 ml methanol for an intensity of 100 units.

compounds exhibited fairly good fluorescence. Relevant electronic absorption and emission data for the compounds synthesised are shown in Table 1.

3 EXPERIMENTAL

All melting points are uncorrected. Several of the compounds gave low analytical values for nitrogen (*ca* 0·5–1%) and a similar behaviour of such heterocyclic systems has been previously noted by Meltzer and coworkers[2] and also in some of our earlier studies.[1]

2-Aceto-1-naphthol was prepared by the method described by Witt and Braun[3] and was converted to the ketoxime (**Ia**) by the method of Michael and Grandmougin.[4]

Compounds **IIa**, **IIIa**, **IVa**, **Va**, **VIa** and **VIIa** were prepared using the method previously reported by us.[1]

3.1 2-[2-(5-Nitronaphth[2,1-*d*]oxazolyl)]malondialdehyde (IIb)

This was prepared by the method employed for the preparation of **IIb**, starting from **Ib**. Thus, phosphorus oxychloride (36 ml, 0·4 mol) was slowly added to dimethylformamide (30 ml, 0·4 mol) at 5–10°C with stirring. After

10 min, a solution of **Ib** (24 g, 0·1 mol) in dimethylformamide (60 ml) was added to the above cooled reagent with stirring. The solution was then heated at 70–80°C for 8 h and then kept overnight at room temperature. It was then poured into ice water (500 ml), treated with 30% sodium hydroxide solution to give pH 10–11 whilst maintaining a temperature of not greater than 60–70°C for 2 h. The mixture was cooled in ice and filtered. The filtrate was acidified with HCl to give a small amount of **IIb** and the residue was extracted repeatedly with hot water to dissolve the sodium salt of **IIb**. This extract on acidification gave **IIb** (27 g, 90%) which was crystallised from alcohol in yellowish brown crystals, m.p. 135°C.

Found: C, 58·8; H, 3·3; N, 9·9%.

$C_{14}H_8N_2O_5$ requires: C, 59·2; H, 2·8; N, 9·9%.

3.2 2-[4-(1-Phenylpyrazolyl)]-5-nitronaphth[2,1-*d*]oxazole (IVb)

This was prepared by a method similar to that for **IIIa**, starting from **IIb**. A mixture of **IIb** (2 g), phenylhydrazone (1 ml) and methanol was refluxed for 1 h (until the mixture failed to give a violet colour with alcoholic $FeCl_3$) and poured into ice water. The brown precipitate was filtered, washed with dilute HCl and dried. Yield 2·1 g (90%), m.p. 242–244°C. It was crystallised from alcohol in brown crystals, m.p. 245°C.

Found: C, 66·9; H, 3·9; N, 15·6%.

$C_{20}H_{12}N_4O_3$ requires: C, 67·4; H, 3·4; N, 15·7%.

3.3 2-[4-(1-Pyrazolyl]-5-nitronaphth[2,1-*d*]oxazole (IIIb)

This was prepared by the method similar to that for **IIIa** starting from **IIb**. Yield 95%, m.p. 170–172°C. It was crystallised from benzene in yellowish brown crystals, m.p. 175°C.

Found: N, 20·5%.

$C_{14}H_8N_4O_3$ requires: N, 20·0%.

3.4 2-[5-(Pyrimidyl)]-5-nitronaphth[2,1-*d*]oxazole (VIb)

This was prepared by the method similar to that for **VIa**, starting from **IIB**. Compound **IIb** (2 g) was refluxed in formamide (20 ml) for 2 h and the solution then added to ice water. The brown product was filtered, washed with water and dried.

Yield 2 g (98%), m.p. 280–283°C. It was crystallised from alcohol in light brown crystals, m.p. 285°C.

Found: N, 18·8%.

$C_{14}H_8N_4O_3$ requires: N, 19·2%.

3.5 2-[5-(2-Phenylpyrimidyl)]-5-nitronaphth[2,1-*d*]oxazole (VIIb)

This was prepared by the method similar to that for **VIIa**, starting from **IIb**. Yield 67%, m.p. 287–290°C. It was crystallised from benzene in brown crystals, m.p. 295°C.

Found: N, 14·7%.

$C_{27}H_{12}N_4O_3$ requires: N, 15·2%.

3.6 2-[5-(2-Phenylaminopyrimidinyl)]-5-nitronaphth[2,1-*d*]oxazole (VIIb)

This was prepared by the method employed for the preparation of **VIIa**, starting from **IIb**. Yield 67%, m.p. 152–154°C. It was recrystallised from alcohol in yellowish brown crystals, m.p. 155°C.

Found: N, 17·7%.

$C_{21}H_{13}N_5O_3$ requires: N, 18·2%.

3.7 2-[4-Pyrazolyl]-5-acetamidonaphth[2,1-*d*]oxazole (IIIc)

To a mixture of acetic acid (15 ml) and acetic anhydride (10 ml), a mixture of **IIIb** (1·0 g) and zinc dust (2·0 g) was added and the mixture refluxed for 1 h. The solution was filtered hot and refluxed with sodium acetate (4·0 g) and acetic anhydride (5·0 ml) for 30 min and then poured into ice water. A yellowish brown precipitate was filtered, washed with water and dried. Yield quantitative, m.p. 161–163°C. It was crystallised from alcohol in yellowish brown crystals, m.p. 165°C.

Found: N, 18·7%.

$C_{16}H_{12}N_4O_2$ requires: N, 19·2%.

3.8 2-[4-(1-Phenylpyrazolyl)]-5-acetamidonaphth[2,1-*d*]oxazole (IVc)

This was prepared by the method employed for the preparation of **IIIc**, starting from **IVb**. Yield quantitative, m.p. 153–155°C. Crystallisation from alcohol gave dark brown crystals, m.p. 157°C.

Found: N, 15·2%.

$C_{22}H_{16}N_4O_2$ requires: N, 15·2%.

3.9 2-[5-Pyrimidyl]-5-acetamidonaphth[2,1-*d*]oxazole (Vc)

This was prepared by the method employed for the preparation of **IIIc**, starting from **Vb**. Yield quantitative, m.p. 300°C. It was crystallised from alcohol in light brown crystals.

Found: N, 18·1%.

$C_{17}H_{12}N_4O_2$ requires: N, 18·4%.

3.10 2-[5-(2-Phenylpyrimidyl)]-5-acetamidonaphth[2,1-*d*]oxazole (VIc)

This was prepared by the method employed for the preparation of **IIIc**, starting from **VIb**. Yield quantitative, m.p. 185–188°C. It was crystallised from alcohol in brown crystals, m.p. 190°C.

Found: N, 14·6%.
$C_{23}H_{16}N_4O_2$ requires: N, 14·7%.

3.11 2-[5-(2-Phenylaminopyrimidyl)]-5-acetamidonaphth[2,1-*d*]oxazole (VIIc)

This was prepared by the method employed for the preparation of **IIIc**, starting from **VIIb**. Yield 50%, m.p. 164–166°C. It was crystallised from benzene in brown crystals, m.p. 168°C.

Found: N, 17·5%.
$C_{20}H_{17}N_5O_2$ requires: N, 17·7%.

ACKNOWLEDGEMENT

We thank Professor M. R. Padhye and Mr V. Raghavendra for the infrared, ultraviolet and fluorescence spectra, and Dr P. K. Inamdar and Mr S. V. Chiplunkar for the microanalytical data.

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