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Studies in the Vilsmeier–Haack Reaction: Part XXV—Synthesis of 3-Hetarylcoumarins by the Application of the Vilsmeier–Haack Reaction†

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SUMMARY

Coumarin-3-acetic acid derivatives have been utilised in the Vilsmeier formylation reaction and the products thus obtained have been converted into 3-hetarylcoumarins, the absorption and emission characteristics of some of which are reported.

1. INTRODUCTION

A large number of coumarin derivatives have been patented for use as fluorescent brighteners and as fluorescent dyes for textile purposes.[1] The main synthetic approach to these compounds utilised so far has involved the use of coumarin-3-carboxylic acid derivatives as starting materials, as in, for example, the synthesis of 3-hetarylcoumarins such as 3-(benzoxazol-2-yl)coumarin,[2] 7-methoxy-3-(5-phenyl-1,3,4-oxadiazol-2-yl)coumarin[3] and 7-methoxy-3-(5-phenyloxazol-2-yl)coumarin.[4] An alternative route has been to condense a hetaryl substituted acetonitrile with an appropriate salicylaldehyde derivative. These methods necessarily limit the range of 3-hetarylcoumarins to heterocycles such as oxazoles,

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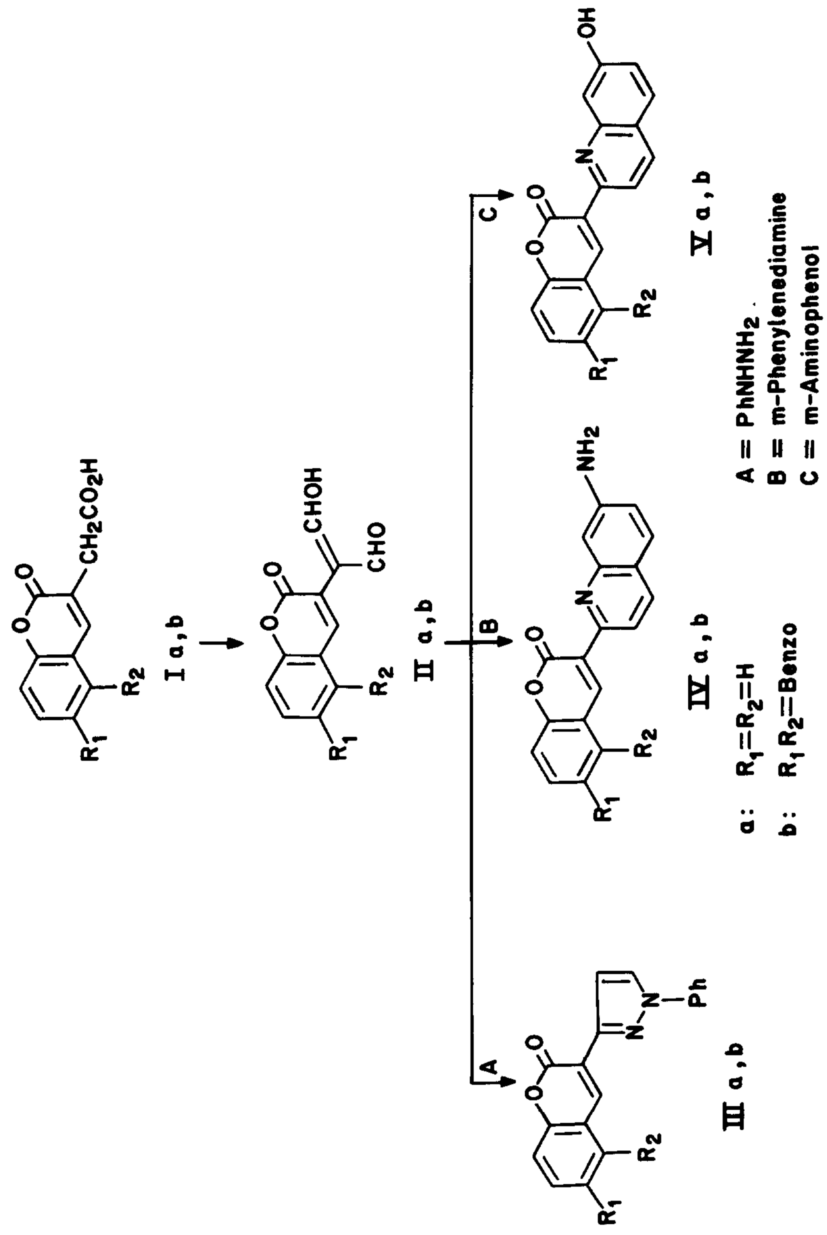

a: $R_1=R_2=H$
b: $R_1R_2=$Benzo

A = $PhNHNH_2$
B = m-Phenylenediamine
C = m-Aminophenol

Scheme 1

imidazoles, oxadiazoles and such compounds as may be obtained by condensation of bifunctional reagents with a carboxylic acid derivative. The use of hetaryl substituted acetonitriles also suffers from the difficulty of preparing the appropriate intermediates.

This paper reports a totally new approach to the synthesis of 3-hetarylcoumarins using coumarin-3-acetic acids as starting materials: their value arises from their facile conversion to the versatile malondialdehydes by the Vilsmeier synthesis.

2. RESULTS AND DISCUSSION

The Vilsmeier–Haack reaction on arylacetic acids to yield the corresponding malondialdehyde derivatives is well known.[5,6] Since the malondialdehydes are versatile intermediates[7,8] it was felt that the Vilsmeier reaction on coumarin-3-acetic acids would provide a convenient approach to the synthesis of different coumarins with a 3-hetaryl substituent. The preparation of some coumarin-3-acetic acids has been reported[9–11] in the literature but these procedures were found in this present work to be unsatisfactory. Whereas in the previously reported syntheses, all the reactants were mixed and heated directly to 180 °C to effect reaction, we found that more satisfactory results were obtained by initial fusion of salicylaldehyde with succinic anhydride, followed by the subsequent addition of sodium succinate with gradual increase in temperature. The availability of coumarin-3-acetic acids thus enables the development of a satisfactory synthesis of the 3-hetaryl coumarins. In this present work, reactions involving the use of coumarin-3-acetic acid (**Ia**) and 5,6-benzocoumarin-3-acetic acid (**Ib**) are described (Scheme 1).

Vilsmeier reaction on the coumarin-3-acetic acids (**Ia** and **Ib**) gave high yields of the corresponding malondialdehydes (**IIa** and **IIb**). These malondialdehydes were characterised by satisfactory elemental analysis; they were readily soluble in cold dilute sodium hydroxide solution and the presence of a β-dicarbonyl function was indicated by a strong violet colour with alcoholic ferric chloride. The malondialdehydes (**IIa** and **IIb**) reacted readily with phenylhydrazine to yield the corresponding 3-(1-phenylpyrazolyl)coumarins **IIIa** and **IIIb** (Table 1). These pyrazoles exhibited an intense bluish violet fluorescence in daylight and were evaluated on polyester by comparison with a standard fluorescent whitener, Uvitex ERN (Ciba–Geigy), at 0·1% w.o.f. on unwhitened

TABLE 1
Physical Data of the 3-Hetarylcoumarins

Compound	*Yield (%)*	*M.p. (°C)*	*Solvent*	*Molecular formula*[a]
1-Phenylpyrazoles				
IIIa	90	224	HOAc	$C_{18}H_{12}N_2O_2$
IIIb	92	226	HOAc	$C_{22}H_{14}N_2O_2$
7-Aminoquinolines				
IVa	62	209	EtOH	$C_{18}H_{12}N_2O_2$
IVb	64	222	EtOH	$C_{22}H_{14}N_2O_2$
7-Hydroxyquinolines				
Va	50	180	EtOH	$C_{18}H_{11}NO_3$
Vb	54	185	EtOH	$C_{22}H_{11}NO_3$

[a] Satisfactory elemental analyses were obtained.

polyester fabric. The whitening effect of compounds **IIIa** and **IIIb** was found to be moderate with respect to the standard. The absorption and fluorescence emission data are given in Table 2.

Naik and Seshadri[12] have previously reported the synthesis of strongly fluorescent 7-amino-3-hetarylquinolines from malondialdehydes and *m*-phenylenediamine. We therefore reacted the malondialdehydes (**IIa** and **IIb**) with *m*-phenylenediamine and with *m*-aminophenol to obtain the corresponding quinolines (**IVa**, **IVb**, **Va** and **Vb**). These compounds showed an intense greenish blue fluorescence in daylight and were therefore not satisfactory for application on polyester as optical brighteners. The UV absorption and fluorescence emission data are given in Table 2.

TABLE 2
Absorption–Emission Data of the 3-Hetarylcoumarins

Compound	*Absorption λ_{max} (nm)*	*log E*	*Fluorescence λ_{max} (nm)*
IIIa	355	4·52	426
IIIb	376	4·52	440
IVa	372	4·13	470
IVb	378	4·27	473
Va	368	4·1	467
Vb	373	4·17	466

3. EXPERIMENTAL

All melting points are uncorrected. The UV and visible spectra were recorded on Beckman DK-2 and Unicam SP 8000 spectrophotometers.

Coumarin-3-acetic acid (Ia)

A mixture of salicylaldehyde (0·12 mol) and succinic anhydride (0·35 mol) was stirred at 90 °C for 30 min. The temperature of the reaction mixture was then raised slowly to 180–185 °C. Dried sodium succinate (0·16 mol) was added slowly with stirring to the above over a period of 4 h. The resultant molten liquor was treated with dilute HCl, filtered and the residue washed free of acid with water. The solid residue was dissolved in $NaHCO_3$ solution (5 %) and filtered. The filtrate was added to cooled HCl(1:1) when coumarin-3-acetic acid precipitated in 40 % yield, m.p. 157–158 °C. (Reported m.p.,[10,11] 157–158 °C).

5,6-Benzocoumarin-3-acetic acid (Ib)

This was prepared using 2-hydroxy-1-naphthaldehyde instead of salicylaldehyde following the above procedure and was obtained in 30 % yield. It was crystallised from EtOH, m.p. 262 °C (reported m.p.[9] 265 °C).

General procedure for the preparation of coumarin-3-malondialdehydes (IIa and IIb)

The coumarin-3-acetic acid derivative (**Ia** or **Ib**) (0·01 mol) was added to the Vilsmeier reagent prepared from DMF (12 ml) and $POCl_3$ (0·026 mol). An additional amount of DMF (12 ml) was added to dissolve the solid that separated from the reaction mixture. The reaction mixture was heated on a waterbath for 6–7 h, cooled and poured into ice-cold water and the liquor then made alkaline with NaOH (10 %) to pH 10–11. The alkaline solution was boiled for 30 min to effect hydrolysis. After cooling and acidifying with HCl (1:1) the corresponding malondialdehyde (**IIa** or **IIb**) was precipitated. Thus, **IIa** was obtained in 87 % yield and was crystallised from aq. HOAc, m.p. 122–4 °C (Found: C, 66·5, H, 3·3; $C_{12}H_8O_4$ requires C, 66·7, H, 3·7 %) and **IIb** was obtained in 70 % yield and was crystallised from aq. HOAc, m.p. 229–233 °C (Found: C, 72·0, H, 4·2; $C_{16}H_{10}O_4$ requires C, 72·2, H, 3·8 %).

General procedure for the preparation of 3-(1-phenylpyrazol-3-yl)coumarin derivatives (IIIa and IIIb)

A mixture of **IIa** or **IIb** (0·01 mol) and phenylhydrazine (0·012 mol) in ethanol (5 ml) containing a drop of HOAc was refluxed for 2 h. The solid which separated was filtered; the yield, melting point, crystallisation solvent and molecular formula of the pyrazolyl coumarins thus prepared are given in Table 1.

General procedure for the preparation of 3-[3-(7-substituted quinolinyl)]-coumarin derivatives (IVa, IVb, Va and Vb)

A mixture of **IIa** or **IIb** (0·001 mol), *m*-phenylenediamine or *m*-aminophenol (0·0012 mol) and *p*-toluenesulphonic acid (0·005 mol) in glacial acetic acid (10 ml) was refluxed for 4 h. The cooled reaction mixture was poured into ice-cold water and neutralised to pH 7–8. The resultant solid was filtered, washed with water and dried. The yield, melting point, crystallisation solvent and molecular formula of the various quinolinylcoumarin derivatives are given in Table 1.

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