

SOLVENT-FREE SYNTHESIS OF SULFONEPHTHALEINS, SULFONEFLUORESCAINS AND FLUORESCAINS UNDER MICROWAVE IRRADIATION

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An efficient solvent-free synthesis of sulfonephthaleins, sulfonefluoresceins and fluoresceins under microwave irradiation is reported.

Keywords: Microwave assisted reactions; Triphenylmethane dyes; Acidobasic indicators; Phthaleins; Green chemistry.

During the last ten years a number of publications have described application of the microwave technique in organic and organometallic synthesis¹. Short reaction times (usually minutes), superb purity of products and enhancement of chemical yields are usually quoted as major advantages of this method. Unfortunately, most experiments have been performed in domestic ovens using classical organic chemistry methodology in solvents. Safety problems were described mainly in connection with low boiling points and high vapour pressures of solvents^{2,3}. This is likely the driving force for application of dry reaction techniques and their coupling with microwaves⁴⁻⁶.

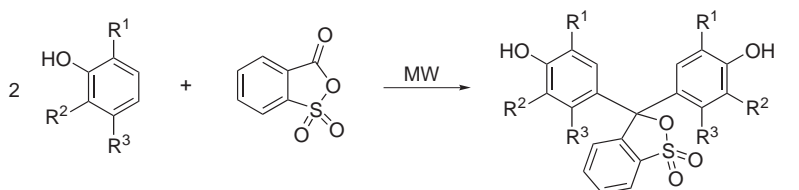
There is an increasing interest in the use of environmentally benign reagents and conditions and particularly in solvent-free procedures⁷. Avoiding organic solvents in organic synthesis leads to a clean, efficient and economical technology. Safety is largely increased, work-up is considerably simplified, cost is reduced, increased amounts of reactants can be used in the same equipment, reactivities and sometimes selectivities are enhanced when working without dilution.

Here we describe the application of solvent-free microwave methodology to the synthesis of sulfonephthaleins and sulfonefluoresceins – well-known representatives of triphenylmethane dyes. The compounds can be considered as complementary, especially with respect to their solubility, chemical

reactivity, and acid-base behaviour. Contrary to sulfonephthaleins, which exist in ionic form, phthaleins themselves are believed to prefer the lactone form. Many methods are described in literature for the synthesis of these compounds, such as simple fusion of both components⁸⁻¹¹, sometimes combined with azeotropic removal of water¹², or fusion in the presence of catalysts, such as POCl_3 ¹³, polyphosphoric acid¹⁴ and $\text{POCl}_3\text{-HClO}_4$ ^{15,16}. The inherent drawbacks of all described synthetic methods are long heating (up to tens of hours) at precisely defined (programmed) temperature(s) and the presence of acidic catalyst(s) necessary for high-yield reaction.

RESULTS AND DISCUSSION

We have found that commercially available monomode MW reactor (MWR) and sometimes even domestic oven (MWO), which is a multimode appliance, can bring about profound enhancement of the efficiency of preparation of these compounds. The reaction times are shortened to tenths of second, which means the enhancement of more than three orders of magnitude. Moreover, the reaction is extremely easy to perform. We have applied this method to the synthesis of compounds **1-17** (Schemes 1-3).

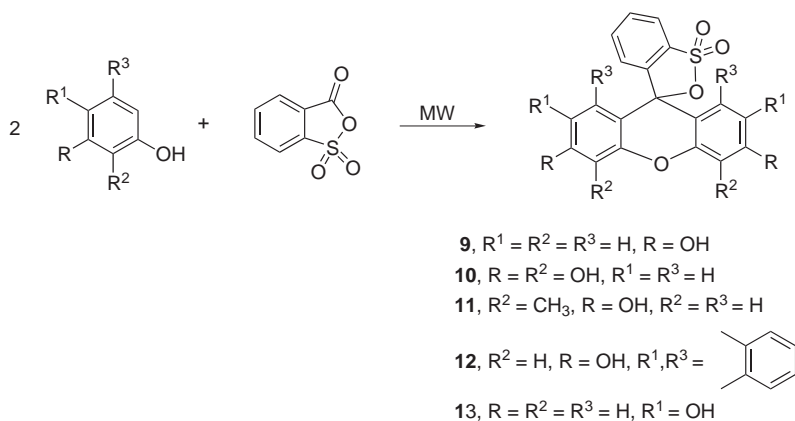


- 1, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$
- 2, $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{R}^3 = \text{H}$
- 3, $\text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{CH}_3$
- 4, $\text{R}^1 = \text{R}^3 = \text{CH}_3, \text{R}^2 = \text{H}$
- 5, $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{H}, \text{R}^3 = (\text{CH}_3)_2\text{CH}$
- 6, $\text{R}^1 = \text{OH}, \text{R}^2 = \text{R}^3 = \text{H}$
- 7, $\text{R}^1 = \text{R}^2 = \text{CH}_3, \text{R}^3 = \text{H}$
- 8, $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{R}^3 = \text{H}$

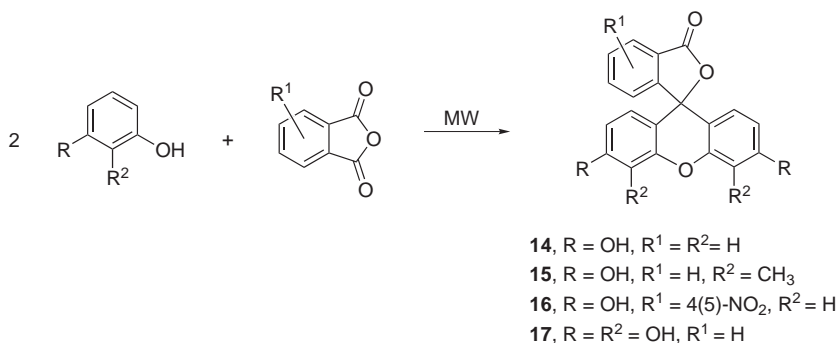
SCHEME 1

Several of them are known compounds, prepared by traditional methods. We have repeated their preparation under MW irradiation. The results obtained are summarised in Table I.

Several new compounds, phthaleins, sulfonephthaleins, and sulfonefluoresceins, have been prepared using this methodology; the results are summarised in Table II.



SCHEME 2



SCHEME 3

It is immediately clear that the reactions performed under MW irradiation are almost instantaneous. We have used both MWO and MWR appliances. The reaction performed in MWO (the simplest procedure) can be easily performed on the 10 g scale. Care has to be taken to the choice of the reaction vessel – as the very important factor is the flat bottom large enough to prevent local overheating in the reaction melt. Usually a standard 750-ml Erlenmeyer flask is large enough to perform reactions in 50–100 g batches. Both solid components have to be powdered and mixed, then placed in the reaction vessel and at least partly melted by application of external heat (also addition of a small amount of an inert solvent (catalyst) can be used to dissolve at least partly the solid mixture). Then MW irradiation (typically 525 W) is applied for a given period. The crude reaction product is boiled with water and isolated, *e.g.*, by precipitation using either known procedures or those described in Experimental.

TABLE I
Microwave synthesis (525 W, 2–5 g batch) of sulfonephthaleins, sulfonefluoresceins and fluoresceins

Compound	Method ^a	Time, s	Solvent or catalyst	R_F^b	Yield, %
1	A	15	–	0.23	82
2	A	12	–	0.29	91 ^c
3	A	10	–	0.34	15
4	A	15	xylene	0.51	55
5	A	15	chlorobenzene	0.59	69
6	A	12	H ₃ PO ₄	0.14	29 ^c
10	A	15	xylene	0.11	77 ^c
10	B	25	xylene	0.11	74
14	B	30	H ₃ PO ₄	0.28	97

^a See the text. ^b Standard TLC (Silufol, pyridine, 4-methylpentan-2-ol, 40% aqueous di-methylamine 1:1:1). ^c Optimised.

TABLE II
Microwave synthesis of sulfonephthaleins and sulfonefluoresceins

Compound	Method ^a	Time, s	Catalyst	R_F^b	Yield, %
7	A	15	xylene	0.63	19
7	A	16	–	0.63	34 ^c
8	A	15	H ₃ PO ₄	0.69	75
9	A	25	H ₃ PO ₄	0.6	66
9	B	35	H ₃ PO ₄	0.6	70
11	B	30	H ₃ PO ₄	0.63	79
12	B	25	H ₃ PO ₄	0.69	23
13	B	30	H ₃ PO ₄	0.60	56
15	B	30	H ₃ PO ₄	0.60	68
16	B	30	H ₃ PO ₄	0.68	82
17	B	25	H ₃ PO ₄	0.53	47

^a See the text. ^b Standard TLC (Silufol, methanol, butanol, water, aqueous ammonia 30:18:4:3). ^c 21% after purification to chromatographically pure substance.

The reaction time is highly dependent on the reactivity of the phenol used. With MWR, all important reaction variables can be controlled and a high level of reproducibility attained. The synthesis of 2,6-xylenolsulfonephthalein (**7**) has been optimised. This new dye was prepared in a MWO in a low yield (Table II). It follows from Fig. 1 that the consumption of energy is high in the first 10–20 s, then the exothermic reaction heats the reaction mixture to temperature above 70 °C in the same period of time and the temperature does not change afterwards (the reaction vessel is placed in the Dewar flask of MWR).

The above data are in agreement with observations and findings obtained when the reaction is performed in MWO. Usually the reaction is finished just before the unreacted phenol and volatile side products start to evaporate. The synthesis of **7** was performed in an optimised way, where the reaction mixture was set aside just before all the inert (xylene) was evaporated and the reaction went to completion without energy uptake. The optimised isolated yield of the pure dye in a MWR 34% was achieved.

In reality, the reaction time is an empirical constant strongly dependent on the MW output and the size of the reaction batch. For phthaleins and sulfonephthaleins, prolonged MW heating is accompanied by electrophilic rearrangement and cyclisation to thermodynamically stable xanthenic derivatives. That is why it is not advisable to perform the reaction at high

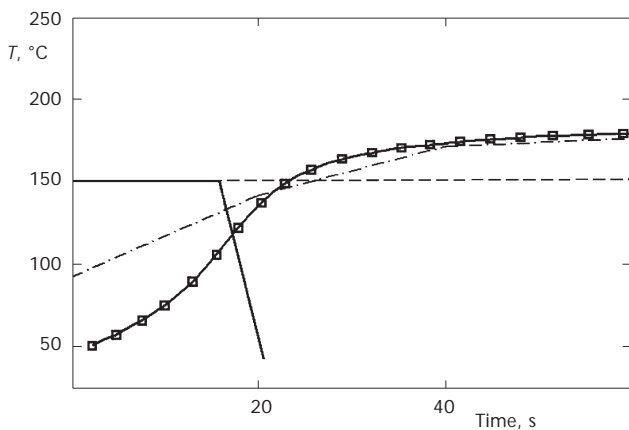


FIG. 1

A typical course of condensation of 2,6-dimethylphenol with 2-sulfo benzoic anhydride in MWR. Critical temperature 250 °C. Irradiation power 40% of the maximum (---); temperature gradient: 0–20, 20–40, 40–60 s (- · - · -); measured temperature (□); irradiation period (—)

MW outputs. Empirically, 40–50% of the maximum output of MWR and 400–550 W of MWO are close to optimum. For fluoresceins and sulfonefluoresceins, however, the reaction can be carried out at a maximum output. Nevertheless, even in these cases, the reaction is complete usually within 15 min at the maximum output (750 W) of MWO.

The temperature of the reaction mixture in MWR measured with IR sensors was found to range between 170 and 180 °C for 7. The temperature measured with a thermoelectric sensor in domestic MWO was around 170 °C, which is in excellent agreement. We have used both 2-sulfobenzoic anhydride and the corresponding free acid in the reactions. Contrary to usual procedures, we have typically used the phenol:anhydride ratio 1:1, which is less economical as the latter is by far the most expensive compound. On the other hand, purification of the reaction mixture is simpler as the separation of phenol excess by time-consuming steam distillation can be avoided. The free acid in the form of their non-stoichiometric hydrates, which is much cheaper and more accessible than the anhydride gives lower yields, probably due to water content in the reaction mixture. Water evaporated during the reaction is assumed to strip off substantial amounts of phenol thus making the reaction conditions difficult to reproduce. This assumption is supported by the fact that with non-volatile resorcinol the reaction proceeds with the same yield regardless of which starting compound is used. As far as the ratio of the starting materials is concerned, we have used two alternatives. Method *A*: 2-sulfobenzoic anhydride:phenol = 1:1. In this method, half of the expensive anhydride is used and lost in binding the reaction water. The equilibrium of the reaction is shifted to the right, to the consumption of phenol. Method *B*: 2-sulfobenzoic anhydride:phenol = 1:2, where the ratio of the reactants is stoichiometric. Accordingly, the high conversion is attainable only if the free acid formed during the reaction is immediately transformed to the starting 2-sulfobenzoic anhydride and water. This reaction takes place only at temperatures above 120 °C, which is too high for less stable dyes. That is why the latter procedure can be used only for very stable fluoresceins and sulfonefluoresceins. An inert solvent is added usually in those cases when the starting mixture of components is solid. Several drops of a solvent (e.g. toluene, xylene or chlorobenzene) were used for a 10-g batch to ensure smooth melting of the reaction mixture.

It can be concluded that MW synthesis of the title compounds is the method of choice, especially for thermostabile compounds.

EXPERIMENTAL

Starting compounds were purchased from Fluka (resorcinol, 2-methylresorcinol, naphthalene-1,3-diol), Lachema Brno (sulfonephthaleins and fluorescein, 2-sulfobenzoic anhydride, 2,5-dimethylphenol, thymol, *m*-cresol, hydroquinone, pyrocatechol, pyrogallol, 5-methylresorcinol, guaiacol) and ICI (2-phenylphenol).

Experiments in MWO were typically performed in open 50-ml (<5 g batches), 250-ml (5–15 g batches) and 750-ml (25–100 g batches) Erlenmeyer flasks placed on the rotating support of MW oven (Calex CMM17 with output control in the range 112–750 W). The MWR experiments were performed in a monomodal MW reactor Prolabo (France) equipped with software Synsoft in an original glass vessel. Chemical shifts are given in ppm (δ -scale), coupling constants (J) in Hz.

General Procedure

Method A. 2-Sulfobenzoic anhydride (10 mmol) and the corresponding phenol (10 mmol) were powdered, mixed with an inert solvent or H_3PO_4 (85%), placed in a 50-ml Erlenmeyer flask and irradiated in MWO using an appropriate output and reaction time. The reaction mixture was diluted with water (20 ml) and boiled by short irradiation at 375 W. Sulfonephthaleins are typically isolated by precipitation from their solution in 5% aqueous NaOH with 15% HCl.

Method B. 2-Sulfobenzoic anhydride or phthalic anhydride (5 mmol) was mixed with a phenol (10 mmol), powdered and irradiated. The isolation of fluoresceins was followed by thorough washing with hot water giving the product of outstanding quality. The given yields are based on 2-sulfobenzoic anhydride.

3,3-Bis(4-hydroxyphenyl)-3H-2,1 λ^6 -benzoxathiole 1,1-Dioxide (Phenol Red, **1**).

Method A (MWO). Phenol (47 g, 0.5 mol) was fused with a heat-gun in a 750-ml Erlenmeyer flask (92 g, 0.5 mol) of finely ground *o*-sulfobenzoic anhydride was added and the resulting mixture was mixed. The flask was then placed in MWO, the output was set at 450 W and irradiation was started. Complete homogenisation took place within several seconds, followed by the colour changing quickly from red to dark red (12–15 s) accompanied by evolution of large amounts of water and phenol. The reaction mixture started to vigorously boil and became more viscous. At this moment, the irradiation was switched off and the reaction mixture was set aside for 2–3 min. Then water (120 ml) was added and the mixture was boiled at the 325 W irradiation output for 3–4 min. Excess phenol was usually stripped off by this procedure. The reaction mixture was cooled, filtered and precipitated. The isolated yield was 72.2 g (81.6%).

3,3-Bis(4-hydroxy-3-methylphenyl)-3H-2,1 λ^6 -benzoxathiole 1,1-Dioxide (*o*-Cresol Red, **2**)

Method A (MWO). A mixture of *o*-cresol (1.08 g, 10 mmol) and 2-sulfobenzoic anhydride (1.84 g, 10 mmol) was placed in a 50-ml Erlenmeyer flask and xylene (0.5 ml) was added. After irradiation in MWO at 525 W for 10–12 s, water (10 ml) was added and the mixture was boiled for several minutes until all cresol reacted. The work-up was similar to that in the preceding procedure. Yield 1.73 g (90.6%).

3,3-Bis(4-hydroxy-2-methylphenyl)-3H-2,1λ⁶-benzoxathiole 1,1-Dioxide (*m*-Cresol Purple, 3)

Method A (MWO). The dye was synthesised from *m*-cresol (3-methylphenol) under the same conditions as Phenol Red (1) using method A in a yield of 15%. The product was identical with commercial sample (Lachema Brno, Czech Republic).

3,3-Bis(4-hydroxy-2,5-dimethylphenyl)-3H-2,1λ⁶-benzoxathiole 1,1-Dioxide (*p*-Xylenol Blue, 4)

Method A (MWO). The dye was prepared in 55% yield from *p*-xylenol (2,5-dimethylphenol) using the method described for Phenol Red (1). The only difference was the addition of a few drops of xylene for a better homogenisation of the reaction mixture. The product was identical with commercial sample (Lachema Brno, Czech Republic).

3,3-Bis(4-hydroxy-5-isopropyl-2-methylphenyl)-3H-2,1λ⁶-benzoxathiole 1,1-Dioxide (Thymol Blue, 5)

Method A (MWO). The dye was prepared in 69% yield from thymol using the procedure described for Phenol Red (1) with addition of a few drops of chlorobenzene for a better homogenisation of the reaction mixture. The product was identical with commercial sample (Lachema Brno, Czech Republic).

3,3-Bis(3,4-dihydroxyphenyl)-3H-2,1λ⁶-benzoxathiole 1,1-Dioxide (Pyrocatechol Violet, 6)

Method A (MWO). The dye was prepared in 29% yield from pyrocatechol using the same conditions as those used for Phenol Red (1) with addition of few drops of 85% H₃PO₄ for a better homogenisation of the reaction mixture and also as a catalyst. The product was characterised by comparison with a commercially available laboratory standard (Lachema Brno, Czech Republic).

3,3-Bis(4-hydroxy-3,5-dimethylphenyl)-3H-2,1λ⁶-benzoxathiole 1,1-Dioxide (2,6-Xylenolsulfonephthalein, 7)

Method A (MWO). The dye was prepared in 19% yield from 2,6-dimethylphenol using the procedure described for Phenol Red (1). A few millilitres (2–5 ml) of xylene as a homogenisation and thermostatic agent was added and the reaction mixture was irradiated for 15 s, followed by another 15 s without irradiation to complete the reaction. The hot reaction mixture was quenched with water, the solid was dissolved in 20% NaOH and precipitated by addition of 15% HCl. This procedure was repeated twice. For C₂₃H₂₀O₅S (408.5) calculated: 67.30% C, 5.40% H, 7.81% S; found: 67.28% C, 5.53% H, 7.67% S. ¹H NMR (D₂O–K₂CO₃): 1.92–1.96 s, 12 H (–CH₃); 6.78–6.82 d, 1 H (arom. H); 6.98–7.00 s, 4H (arom. H); 7.50–7.56 t, 1 H (arom. H); 7.56–7.62 t, 1 H (arom. H); 7.92–7.96 d, 1 H (arom. H).

Method A (MWR). An appropriate temperature gradient was set (*cf.* Fig. 1, reaction time 60 s, 40% reactor output, critical temperature 180–250 °C). A mixture of 2-sulfobenzoic anhydride (1.84 g, 0.01 mol) and 2,6-dimethylphenol (1.32 g, 0.01 mol) was partly fused with a heat-gun in 20-ml reaction vessel, placed in MWR, rotation was switched on and irradiation started. The hot reaction mixture was then diluted with water (5 ml) followed by 20% aqueous NaOH (5 ml). Precipitation of the dye was performed by addition of 15% HCl and this procedure was repeated twice. The chromatographically pure compound 0.86 g (21%)

was collected. For $C_{23}H_{20}O_5S$ (408.5) calculated: 67.30% C, 5.40% H, 7.81% S; found: 67.28% C, 5.53% H, 7.67% S. 1H NMR ($D_2O-K_2CO_3$): 1.92–1.96 s, 12 H ($-CH_3$); 6.78–6.82 d, 1 H (arom. H); 6.98–7.00 s, 4 H (arom. H); 7.50–7.56 t, 1 H (arom. H); 7.56–7.62 t, 1 H (arom. H); 7.92–7.96 d, 1 H (arom. H).

3,3-Bis(4-hydroxy-3-phenylphenyl)-3*H*-2,1 λ^6 -benzoxathiole 1,1-Dioxide
(2-Phenylphenolsulfonephthalein, **8**)

Method A (MWO). The product was prepared in 75% yield analogously to Phenol Red (**1**) from 2-phenylphenol using a few drops of concentrated H_3PO_4 . For $C_{31}H_{20}O_5S$ (504.6) calculated: 73.50% C, 4.38% H, 6.33% S; found: 73.09% C, 4.53% H, 6.08% S. 1H NMR ($D_2O-K_2CO_3$): 6.46–6.54 d, 1 H (arom. H); 7.02–7.40 m, 14 H (arom. H); 7.42–7.50 t, 1 H (arom. H); 7.52–7.60 t, 1 H (arom. H); 7.82–7.92 d, 1 H (arom. H).

2-(6-Hydroxy-3-oxo-3*H*-xanthen-9-yl)benzene-1-sulfonic Acid (Sulfonefluorescein, **9**)

Method A (MWO). The dye was prepared in 66% yield from resorcinol and 2-sulfobenzoic anhydride using general method A with the addition of few drops of 85% H_3PO_4 . The sulfonefluorescein could not be analysed by combustion due to sublimation at high temperatures. 1H NMR ($D_2O-K_2CO_3$): 6.44–6.46 s, 2 H (arom. H); 6.48–6.52 d, 2 H (arom. H); 6.84–6.88 d, 2 H (arom. H); 6.90–6.94 d, 1 H (arom. H); 7.52–7.56 t, 1 H (arom. H); 7.62–7.68 t, 1 H (arom. H); 7.98–8.02 d, 1 H (arom. H).

Method B (MWO). A mixture of resorcinol (1.1 g, 10 mmol) and 2-sulfobenzoic anhydride (0.92 g, 5 mmol) with several drops of 85% H_3PO_4 in a 50-ml Erlenmeyer flask was irradiated at 640 W for 15 s. The semisolid mixture was then diluted with water (25 ml), NaOH (0.8 g) was added and the mixture was boiled until everything dissolved (several minutes). The product was precipitated by careful addition of 10% aqueous HCl (50 ml). The suspension was boiled for a while, then hot-filtered, washed with hot water, collected and dried to yield 1.3 g (70%) of **9**. The sulfonefluorescein could not be analysed by combustion due to sublimation at high temperatures. 1H NMR ($D_2O-K_2CO_3$): 6.44–6.46 s, 2 H (arom. H); 6.48–6.52 d, 2 H (arom. H); 6.84–6.88 d, 2 H (arom. H); 6.90–6.94 d, 1 H (arom. H); 7.52–7.56 t, 1 H (arom. H); 7.62–7.68 t, 1 H (arom. H); 7.98–8.02 d, 1 H (arom. H).

2,4,5,6,7-Pentahydroxy-3-oxo-3*H*-xanthen-9-yl)benzene-1-sulfonic Acid
(Pyrogallol Red, **10**)

Method A (MWO). The dye was prepared in 77% yield from pyrogallol using the same procedure as described for Phenol Red (**1**) with addition of a few drops of xylene for a better homogenisation of the reaction mixture. The product was identical with commercial laboratory standard (Lachema Brno, Czech Republic).

2-(6-Hydroxy-5,6-dimethyl-3-oxo-3*H*-xanthen-9-yl)benzene-1-sulfonic Acid
(Methylsulfonefluorescein, **11**)

Method B (MWO). The dye was prepared in 79% yield from 2-methylresorcinol and 2-sulfobenzoic anhydride using the procedure described for **9**. Methylsulfonefluorescein could not be analysed by combustion due to sublimation at high temperatures. 1H NMR ($D_2O-K_2CO_3$): 1.92–1.94 s, 6 H ($-CH_3$); 6.48–6.52 d, 2 H (arom. H); 6.84–6.88 d, 2 H (arom. H);

6.90–6.94 d, 1 H (arom. H); 7.52–7.56 t, 1 H (arom. H); 7.64–7.68 t, 1 H (arom. H); 7.98–8.02 d, 1 H (arom. H).

2-(9-Hydroxy-5-oxo-5*H*-dibenzo[*a,j*]xanthen-14-yl)benzene-1-sulfonic Acid
(Naphthosulfonefluorescein, **12**)

Method B (MWO). The dye was prepared in 23% yield from naphthoresorcinol (naphthalene-1,3-diol) and 2-sulfobenzoic anhydride analogously to sulfonefluorescein (**9**). Naphthosulfonefluorescein could not be analysed by combustion due to sublimation at high temperatures. $^1\text{H NMR}$ ($\text{D}_2\text{O}-\text{K}_2\text{CO}_3$): 6.44–6.46 s, 2 H (arom. H); 6.48–6.52 d, 2 H (arom. H); 6.72–6.7 t, 2 H (arom. H); 6.84–6.88 d, 2 H (arom. H); 6.90–6.94 d, 1 H (arom. H); 6.98–7.02 d, 2 H (arom. H); 7.06–7.12 t, 2 H (arom. H); 7.20–7.24 d, 2 H (arom. H); 7.52–7.56 t, 1 H (arom. H); 7.62–7.68 t, 1 H (arom. H); 7.98–8.02 d, 1 H (arom. H).

2-(2,7-Dihydroxy-9*H*-xanthen-9-ylum-9-yl)benzene-1-sulfonate
(Hydroquinonesulfonefluorescein, **13**)

Method B (MWO). The dye was prepared in 56% yield from hydroquinone and 2-sulfobenzoic anhydride using the procedure described for sulfonefluorescein (**9**). The hydroquinonesulfonefluorescein could not be analysed by combustion due to sublimation at high temperatures. $^1\text{H NMR}$ ($\text{D}_2\text{O}-\text{K}_2\text{CO}_3$): 6.42–6.44 s, 2 H (arom. H); 6.48–6.52 d, 2 H (arom. H); 6.82–6.86 d, 2 H (arom. H); 6.90–6.94 d, 1 H (arom. H); 7.52–7.56 t, 1 H (arom. H); 7.62–7.56 t, 1 H (arom. H); 7.98–8.02 d, 1 H (arom. H).

2-(6-Hydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic Acid (Fluorescein, **14**)

Method B (MWO). Fluorescein was synthesised from resorcinol and phthalic anhydride using general method *B*, irradiation 30 s, with addition of few drops of 85% H_3PO_4 . The yield was 97% (optimised, based on anhydride). The product was identical with commercial standard (Lachema Brno, Czech Republic).

2-(6-Hydroxy-4,5-dimethyl-3-oxo-3*H*-xanthen-9-yl)benzoic Acid
(4,5-Dimethylfluorescein, **15**)

Method B (MWO). From 2-methylresorcinol (248 mg, 2 mmol), phthalic anhydride (148 mg, 1 mmol) and one drop of 85% H_3PO_4 (MWO, 350 W, 30 s), compound **15** (230 mg, 68%) was isolated using repeated precipitation from aqueous ammonia. For $\text{C}_{22}\text{H}_{16}\text{O}_5$ (360.4) calculated: 73.33% C, 4.48% H, 22.20% O; found: 72.98% C, 4.60% H, 22.52% O. $^1\text{H NMR}$ ($\text{D}_2\text{O}-\text{K}_2\text{CO}_3$): 1.92–2.00 s, 6 H ($-\text{CH}_3$); 6.56–6.62 d, 2 H (arom. H); 6.68–6.74 d, 2 H (arom. H); 7.22–7.28 d, 1 H (arom. H); 7.48–7.62 m, 2 H (arom. H); 7.70–7.76 d, 1 H (arom. H).

2-(6-Hydroxy-3-oxo-3*H*-xanthen-9-yl)-4(5)-nitrobenzoic Acid; A Mixture of Isomers
(4'(5')-Nitrofluorescein, **16**)

Method B (MWO). The dye was prepared in 82% yield from 4-nitrophthalic anhydride and resorcinol with a catalytic amount of H_3PO_4 analogously to the 4,5-dimethylfluorescein (**15**) procedure. For $\text{C}_{20}\text{H}_{11}\text{NO}_7$ (377.3) calculated: 63.67% C, 2.94% H, 3.71% N; found: 63.41% C, 2.98% H, 3.63% N. $^1\text{H NMR}$ ($\text{D}_2\text{O}-\text{K}_2\text{CO}_3$): 6.48–6.54 s, 2 H (arom. H); 6.56–6.62 d, 2 H

(arom. H); 6.68–6.74 d, 2 H (arom. H); 7.22–7.26 d, 1 H (arom. H); 7.52–7.58 d, 1 H (arom. H); 7.74–7.78 s, 1 H (arom. H).

(4,5,6-Trihydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic Acid (Gallein, 17)

Method B (MWO). The dye was prepared in 47% yield from phthalic anhydride and pyrogallol with a catalytic amount of H_3PO_4 analogously to the 4,5-dimethylfluorescein procedure (15). For $C_{20}H_{12}O_7$ (364.3) calculated: 65.94% C, 3.32% H; found: 65.69% C, 3.42% H. 1H NMR ($D_2O-K_2CO_3$): 6.56–6.62 d, 2 H (arom. H); 6.68–6.74 d, 2 H (arom. H); 7.22–7.28 d, 1 H (arom. H); 7.48–7.62 m, 2 H (arom. H); 7.70–7.76 d, 1 H (arom. H).

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