

## Improved Synthesis of Thiofluorescein

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**Abstract**—Thiofluorescein was synthesized in a preparative yield by successive demethylation of 3,3'-dimethoxydiphenyl sulfide to 3,3'-dihydroxydiphenyl sulfide and condensation of the latter with phthalic anhydride in H<sub>2</sub>SO<sub>4</sub>. The title compound was also obtained in a higher yield from 3,3'-dimethoxydiphenyl sulfide directly in a one-pot process combining the condensation in H<sub>2</sub>SO<sub>4</sub> and demethylation in 2 Py · H<sub>2</sub>SO<sub>4</sub>.

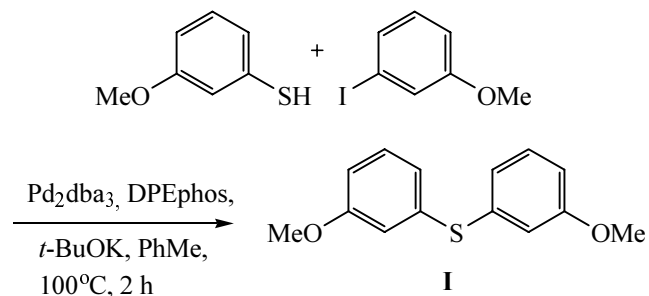
Bromo- and iodo-substituted xanthene dyes are used in photopolymerization processes [1–4] due to high yield of the triplet state which gives rise to effective electron transfer from the donor molecule with formation of free radicals. Analogous increase in the yield of the triplet excited state is attained by replacement of the ring oxygen atom in Fluorescein by sulfur (Thiofluorescein) [5].

A reliable synthesis of Thiofluorescein (3',6'-dihydroxy-3*H*-spiro[2-benzofuran-1,9'-[9*H*]thioxanthen]-3-one) was reported for the first time in patent [6]. 3,3'-Dimethoxydiphenyl sulfide (**I**) obtained by reaction of sodium 3-methoxybenzenethiolate with 3-iodo-1-methoxybenzene was demethylated to 3,3'-dihydroxydiphenyl sulfide (**II**), and the latter was brought into condensation with phthalic anhydride in 80% sulfuric acid. However, neither the yield nor other parameters of the condensation product were given. According to Pfoertner [7], the condensation of sulfide **II** with phthalic anhydride was performed in molten ZnCl<sub>2</sub>, but no experimental procedure was given. El'tsov *et al.* [5] synthesized Thiofluorescein (**III**) using as starting compound sulfide **I** rather than **II**. The condensation and demethylation stages were combined into a one-pot process which was carried out in 80% sulfuric acid. The target product was isolated in 32% yield after triple reprecipitation, washing, dissolution, filtration, and additional purification. The product was characterized only by the analytical data (C, H) and molar absorption coefficient in a sodium hydroxide solution.

The goal of the present work was to experimentally check the above procedures for the synthesis of Thiofluorescein (**III**) and improve them using both methoxy sulfide **I** and hydroxy sulfide **II** as initial compound. The first stage in the synthesis of Thiofluorescein (**III**) is preparation of sulfides **I** and **II**. According to the data of [5–7], sulfide **I** was obtained by heating a mixture of sodium-3-methoxybenzenethiolate with 3-iodo-1-methoxybenzene (Scheme 1) above 200°C in the presence of copper powder [8]. Our attempts to reproduce this procedure showed that the yield of sulfide **I** does not exceed 52%. Schopfer and Schlapback [9] proposed to use tris(dibenzylideneacetone)dipalladium Pd<sub>2</sub>(dba)<sub>3</sub> as efficient catalyst for analogous condensations. Under the conditions reported in [9] [100°C, Pd<sub>2</sub>(dba)<sub>3</sub>], we synthesized sulfide **I** in 80% yield.

Demethylation of **I** was effected [6, 7] by treatment with hydrogen iodide in acetic acid. We applied a more

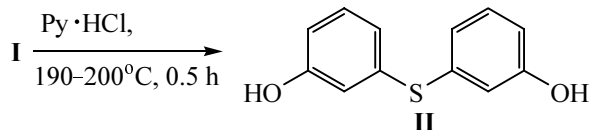
Scheme 1.



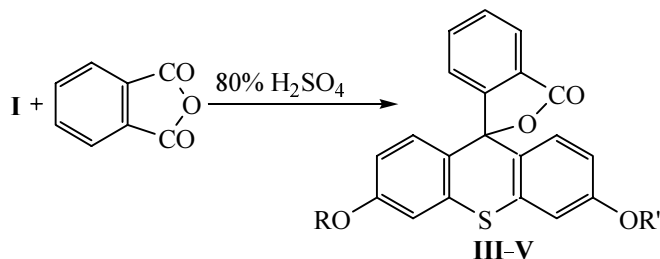
DPEphos is 2,2'-bis(diphenylphosphino)diphenyl ether.

<sup>†</sup> Deceased.

Scheme 2.



Scheme 3.



III, R = R' = H; IV, R = Me, R' = H; V, R = R' = Me.

efficient procedure reported for methyl phenyl ethers [10], according to which methoxy sulfide **I** was hydrolyzed with the system pyridine–HCl; the reaction was performed at 190–200°C, and hydroxy sulfide was obtained in 87% yield (Scheme 2). It should be noted that compound **II** can be prepared directly from less expensive and more accessible materials, 3-chlorophenol and hydrogen sulfide [11] (yield 50–60%). However, this procedure requires a special apparatus ensuring recycling through the reaction zone heated to 500–560°C.

As the second stage in the synthesis of Thiofluorescein (**III**) we initially examined the condensation of dimethoxy sulfide **I** with phthalic anhydride in 80% sulfuric acid according to Scheme 3 (as proposed in [5]) without preliminary conversion of **I** into hydroxy derivative **II**

Condensation of diphenyl sulfides **I** and **II** with phthalic anhydride and subsequent demethylation of the condensation products

Run no.	Initial sulfide	Temperature, °C	Time, h	Yield, %		
				III	IV	V
1	I	20 to 60 <sup>a</sup>	1	14	15	7
2	I	160 <sup>a</sup>	1	16	13	6
3	I	160 <sup>a</sup>	2	7	6	3
4	II	150 <sup>a</sup>	1	74	–	–
5	I	150 <sup>a, b</sup>	1	63	–	–
6	I	150 <sup>a, c</sup>	1	76	1	–

<sup>a</sup> 80% sulfuric acid.

<sup>b</sup> Subsequent demethylation with Py · HCl at 190–200°C (0.5 h).

<sup>c</sup> Subsequent demethylation with 2Py · H<sub>2</sub>SO<sub>4</sub> at 190–200°C (0.5 h).

(see table). After washing to remove H<sub>2</sub>SO<sub>4</sub>, the product was a mixture of compounds. By column chromatography we succeeded in isolating Thiofluorescein (**III**) and its mono- and dimethyl ethers **IV** and **V** in 14, 15, and 7% yield, respectively (see table, run no. 1). We failed to raise the fraction of **III** among the products by varying the temperature from 150 [6] to 160°C [5] and reaction time from 1 to 2 h (run nos. 1–3). On the other hand, by condensation of dihydroxy sulfide **II** with phthalic anhydride in 80% sulfuric acid (i.e., under the conditions described in [6]) we obtained Thiofluorescein in 74% yield (run no. 4). Thus the main obstacle to prepare Thiofluorescein in a good yield according to Scheme 3 [5] is the low efficiency of sulfuric acid as demethylating agent. Nevertheless, this approach seems to be attractive, for it ensures preparation of the target product directly from methoxy sulfide **I** without isolation of intermediate hydroxy sulfide **II**.

In order to improve the yield of compound **III** according to Scheme 3, the resulting mixture of condensation products **III–V** was subjected to demethylation by heating with pyridine hydrochloride for 0.5 h at 190–200°C. As a result, Thiofluorescein (**III**) was isolated in 63% yield (run no. 5). Furthermore, we found that the condensation and demethylation of the condensation products can be effected in a one-pot process. For this purpose, it is necessary to add pyridine (in an amount required to obtain 2Py · H<sub>2</sub>SO<sub>4</sub>) to the mixture in 80% H<sub>2</sub>SO<sub>4</sub> and to heat the mixture for 0.5 h at 190–200°C. In such a way we succeeded in isolating 76% of Thiofluorescein (**III**) (run no. 6). The purity of the isolated substances was checked by elemental analysis and <sup>1</sup>H NMR and electron absorption spectra.

Thus successive demethylation of sulfide **I** and condensation of sulfide **II** with phthalic anhydride gives Thiofluorescein (**III**) in 74% yield (calculated on sulfide **II**; 64% calculated on dimethoxy sulfide **I**). Thiofluorescein (**III**) can be obtained in 76% yield directly from sulfide **I** according to Scheme 3 with additional demethylation by 2Py · H<sub>2</sub>SO<sub>4</sub>.

## EXPERIMENTAL

The IR spectra were recorded on a Vector 22 spectrometer in KBr. The electron absorption spectra were measured on a Hewlett–Packard 8453 spectrophotometer. The <sup>1</sup>H NMR spectra were obtained on a Bruker WP-200SY instrument at 200.13 MHz using chloroform as internal reference. The mass spectra

(electron impact, 70 eV) were run on a Finnigan MAT 8200 mass spectrometer. Column chromatography was performed on KSK silica gel. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates.

3-Methoxybenzenethiol (98%, Aldrich) and 3-iodo-1-methoxybenzene (98%, Lancaster) were used without additional purification.

3,3'-Dimethoxydiphenyl sulfide (**I**) was synthesized in 52% yield by the procedure reported in [8] and in 80% yield by the procedure described in [9]. bp 155°C (2 mm); published data [8]: bp 214–215°C (10 mm). <sup>1</sup>H NMR spectrum (CCl<sub>4</sub>), δ, ppm: 3.64 s (6H, OMe), 6.63 d.m (2H, 4-H, 4'-H, *J* = 7.2, 2.5 Hz), 6.75–6.84 m (4H, 2-H, 2'-H, 6-H, 6'-H), 7.07 t (2H, 5-H, 5'-H, *J* = 7.7 Hz).

3,3'-Dihydroxydiphenyl sulfide (**II**) was obtained by demethylation of sulfide **I** under the conditions reported in [10]. Yield 87%, mp 128–129°C (from CHCl<sub>3</sub>); published data [11]: mp 129–130°C. <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: 4.6–6.1 br.s (2H, OH), 6.67 d.m (2H, 4-H, 4'-H, *J* = 8.6, 2.4 Hz), 6.76 t (2H, 2-H, 2'-H, *J* = 1.8 Hz), 6.90 d.m (2H, 6-H, 6'-H, *J* = 7.9 Hz), 7.17 t (2H, 5-H, 5'-H, *J* = 7.9 Hz).

**Condensation of compounds I and II with phthalic anhydride.** Compound **I**, 2.46 g (0.01 mol), or **II**, 2.16 g (run no. 4), and 1.48 g (0.01 mol) of sublimed phthalic anhydride were dissolved in 5 ml of 80% sulfuric acid, and the mixture was heated for 1 h at 20 to 160°C (run no. 1) or kept for 1 or 2 h at 150 or 160°C (run nos. 2–4). The mixture was cooled to room temperature and poured into 100 ml of water. The brown precipitate was filtered off, washed with 70 ml of water, and dried in air. The product, 3.5 g, was ground in a mortar with 5 g of silica gel (0–140 μm) and washed with 50 ml of diethyl ether on a filter; this procedure was repeated three times. The solvent was distilled off, and the residue was ground in a mortar with 5 g of silica gel, and the resulting material was applied to a column charged with silica gel (140–315 μm, 2 × 30 cm). The column was eluted in succession with benzene, chloroform, and diethyl ether (run nos. 1–3) or with diethyl ether (run no. 4). The separation process was monitored by TLC using diethyl ether–benzene (4 : 1, by volume) as eluent. Three fractions were collected (benzene–chloroform, chloroform–diethyl ether, and diethyl ether), which corresponded to one yellow and two orange spots on Silufol plates. In run no. 4, only one fraction was obtained (orange spot).

**Thiofluorescein (3',6'-dihydroxy-3*H*-spiro[2-benzofuran-1,9']-[9*H*]thioxanthen]-3-one) (**III**)** was

isolated from the third fraction (eluent diethyl ether) by removal of the solvent and washing of the residue with chloroform on a filter. The product was dried over P<sub>2</sub>O<sub>5</sub> at 100°C under reduced pressure. Orange powder, mp 98–102°C. Electron absorption spectrum, λ<sub>max</sub>, nm (log ε): in 0.1 N NaOH: 272 (4.60), 330 (3.71), 512 (4.68); in 0.1 N KOH: 513 (4.57) [5]; published data [7], λ<sub>max</sub>, nm (log ε): 512 (4.69) (0.1 N NaOH). IR spectrum, ν, cm<sup>-1</sup>: 1726, 1596, 1293, 1216. <sup>1</sup>H NMR spectrum (CD<sub>3</sub>OD), δ, ppm: 6.61 d.d (2H, 2'-H, 7'-H, *J* = 8.7, 2.5 Hz), 6.83 d (2H, 1'-H, 8'-H, *J* = 8.7 Hz), 6.95 d (2H, 4'-H, 5'-H, *J* = 2.5 Hz), 7.57 d.m (1H, 7-H, *J* = 7.6 Hz), 7.58–7.77 m (2H, 5-H, 6-H), 7.96 d (1H, 4-H, *J* = 7.5 Hz). Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 348 (3) [*M*]<sup>+</sup>, 304 (31), 303 (48), 104 (20), 76 (24), 45 (20), 32 (25), 31 (50), 28 (100). Found, %: C 68.61; H 3.40; S 9.20. C<sub>20</sub>H<sub>12</sub>O<sub>4</sub>S. Calculated, %: C 68.95; H 3.47; S 9.21.

**3'-Hydroxy-6'-methoxy-3*H*-spiro[2-benzofuran-1,9']-[9*H*]thioxanthen]-3-one (**IV**)** was isolated from the second fraction by removal of the solvent and washing of the residue with carbon tetrachloride on a filter. The product was dried over P<sub>2</sub>O<sub>5</sub> at 100°C under reduced pressure. Yellow powder, mp 115–120°C. Electron absorption spectrum, λ<sub>max</sub>, nm (log ε): in 0.1 N KOH: 289 (4.04), 417 (3.52), 491 (3.58), 511 (3.59); in EtOH: 289 (4.07). IR spectrum, ν, cm<sup>-1</sup>: 1724, 1598, 1288, 1246. <sup>1</sup>H NMR spectrum (CD<sub>3</sub>OD), δ, ppm: 3.76 s (3H, OMe), 6.61 d.d and 6.69 d.d (2H, 2'-H, 7'-H, *J* = 8.7, 2.5 Hz), 6.85 d and 6.91 d (2H, 1'-H, 8'-H, *J* = 8.6 Hz), 6.94 d and 7.04 d (2H, 4'-H, 5'-H, *J* = 2.5 Hz), 7.57 d.m (1H, 7-H, *J* = 7.6 Hz), 7.60–7.77 m (2H, 5-H, 6-H), 7.95 d (1H, 4-H, *J* = 7.5 Hz). Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 362 (14) [*M*]<sup>+</sup>, 319 (25), 318 (59), 317 (100), 303 (26), 287 (42), 274 (44), 45 (36), 31 (75), 28 (55). Found, %: C 69.53, 69.23; H 3.60, 3.67; S 8.82, 8.50. C<sub>21</sub>H<sub>14</sub>O<sub>4</sub>S. Calculated, %: C 69.60; H 3.89; S 8.85.

**3',6'-Dimethoxy-3*H*-spiro[2-benzofuran-1,9']-[9*H*]thioxanthen]-3-one (**V**)** was isolated from the first fraction by removal of the solvent (CHCl<sub>3</sub>+C<sub>6</sub>H<sub>6</sub>) and washing of the residue with methanol on a filter. Colorless powder, mp 191–193°C. Electron absorption spectrum (EtOH), λ<sub>max</sub>, nm (log ε): 204 (4.72), 230 (4.68), 274 (3.99). IR spectrum, ν, cm<sup>-1</sup>: 1777, 1597, 1578, 1486, 1461, 1440, 1404, 1288, 1265. <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>), δ, ppm: 3.78 s (6H, OMe), 6.67 d.d (2H, 2'-H, 7'-H, *J* = 8.5, 2.7 Hz), 6.98 d (2H, 4'-H, 5'-H, *J* = 2.7 Hz), 7.04 d (2H, 1'-H, 8'-H, *J* = 8.5 Hz), 7.49–7.65 m (3H, 5-H, 6-H, 7-H), 7.93 d.m (1H, 4-H, *J* = 7.5 Hz). Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 376 (19) [*M*]<sup>+</sup>,

332 (63), 331 (52), 317 (52), 301 (100), 245 (31), 28 (69). Found, %: C 70.14; H 4.33; S 8.40.  $C_{22}H_{16}O_4S$ . Calculated, %: C 70.21; H 4.26; S 8.51.

**Demethylation of compounds IV and V.** *a. Run no. 5.* A 3.5-g portion of the crude condensation product obtained from dimethoxy sulfide **I** and phthalic anhydride was mixed with 10 g of  $Py \cdot HCl$  [10], and the mixture was stirred for 0.5 h at 190–200°C in a stream of argon. The mixture was cooled and diluted with 100 ml of water, and the red–brown precipitate was filtered off, washed with water, and dried in air. The product, 3.2 g, was ground in a mortar with 5 g of silica gel and extracted with diethyl ether to isolate Thiofluorescein (**III**).

*b. Run no. 6.* A mixture of 2.46 g (0.01 mol) of compound **I** and 1.48 g (0.01 mol) of phthalic anhydride in 5 ml of 80% sulfuric acid was heated for 1 h at 150°C. The mixture was cooled to room temperature, and 13 ml of pyridine was added dropwise under vigorous stirring. The mixture was heated to 190–200°C, kept for 0.5 h at that temperature in a stream of argon, cooled, and diluted with 150 ml of water. The precipitate was filtered off, washed with water, and dried in air. Yield of the crude product 3.5 g. Thiofluorescein (**III**) was isolated from the crude product as described above. Methyl ether **IV** was isolated by evaporation of the chloroform filtrate obtained by washing of compound **III**.

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