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SOLVENT-FREE ONE-POT SYNTHESIS OF SULFONEPHTHALEINS FROM SACCHARIN AND PHENOLS

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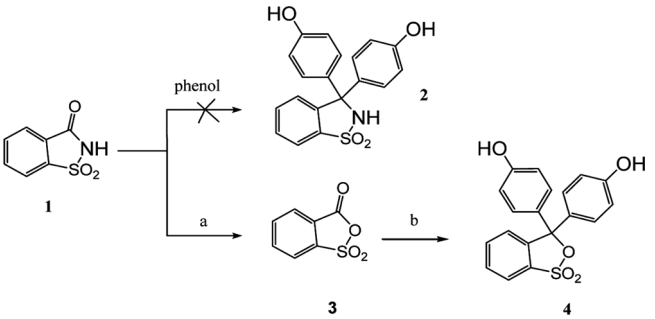
GRAPHICAL ABSTRACT



Abstract *Sulfonephthaleins can be synthesized in a single pot from saccharin and phenol* via *the* in situ *formation of 2-sulfobenzoic anhydride, followed by its reaction with phenol using* H_2SO_4 *as the condensing agent, in the absence of any solvent. This solvent-free synthesis is more economical and environmentally benign.*

Keywords H_2SO_4; phenols; saccharin; sulfonephthalein

INTRODUCTION

The sulfonepthaleins constitute an interesting group of compounds. Since the discovery of sulfonefluorescein and the first synthesis of these compounds by Remsen and his coworkers in 1884,[1] they have been used extensively both as indicators and as diagnostic aids in clinical and experimental medicine. The sulfonephthaleins in general and phenolsulfonephthaleins in particular have been extensively used as a means of testing the renal function, because they are eliminated

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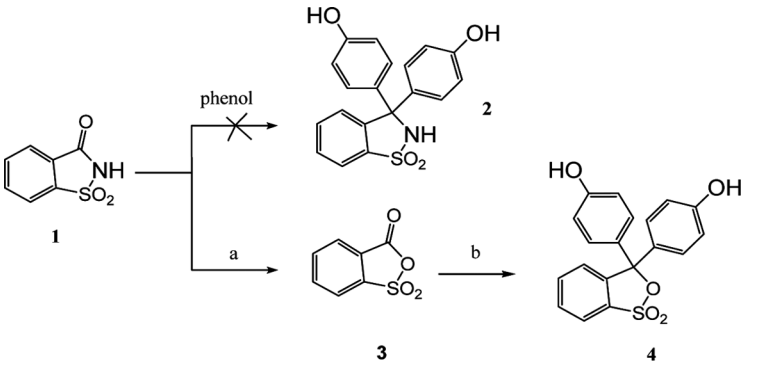
from the blood stream after intravenous injection almost quantitatively through the kidneys.[2] Sulfonephthaleins such as bromophenol blue and bromocresol purple are used for the extractive-spectrophotometric determination of antibiotics such as ofloxacin, cinnarazine, enoxacin, and cisapride in bulk and dosage forms. These methods are based on the formation of yellow ion-pair complexes between the basic nitrogen of the drug and sulfonephthalein dyes, which were extracted in chloroform. The absorbance was measured spectrophotometrically in the range of 408–412 nm.[3–5]

Though sulfonephthaleins are used widely, there are only a few reports about their synthesis. Harden and Drake[6] synthesized a number of sulfonephthaleins having four halogens in the *o*-sulfobenzoic acid part of the molecules. The sulfonephthaleins were prepared by the addition of halogenated *o*-sulfobenzoic anhydride to phenols heated at 110 °C followed by addition of fuming stannic chloride and heating at 120–140 °C for a period of 4–12 h; the sulfonephthaleins were obtained in poor yields, however.

Ondarff and Vose[7] reported that sulfonefluorescein can be prepared by heating dihydroxylbenzoyl-benzene-*o*-sulfonic acid at 160–170 °C for 2 h by eliminating *o*-sulfobenzoic anhydride and water. Hydroxyhydroquinolsulfonephthalein was synthesized by heating *o*-sulfobenzoic acid chloride with hydroxylhydroquinol.[8] In the detailed study for preparation of *m*-cresol sulfonephthalein, Orndarff and Purdy[9] found that the products of the condensation of *m*-cresol with *o*-sulfobenzoic acid anhydride depend on the temperature of the reaction.

Considering the importance of the phenolsulfonephthalein group of compounds as indicators and diagnostic aids in clinical fields, development of a better synthetic method for these compounds is very important. The main purpose of this study was to use readily available saccharin as the starting material instead of *o*-sulfobenzoic acid or anhydride in the synthesis of sulfonephthaleins. In this communication, we report a two-step synthesis of phenolsulfonephthalein from saccharin and phenol in a single pot, using H_2SO_4 as the condensing agent, as described in Scheme 1. In the first step, saccharin (**1**) is converted to *o*-sulfobenzoic anhydride (**3**) which on reaction with phenol is converted to a corresponding



Scheme 1. Synthesis of phenolsulfonephthalein from saccharin and phenol: (a) conc. H_2SO_4/oleum, 140 °C, 3 h; (b) phenol, conc. H_2SO_4, 140 °C, 3 h.

o-sulfonephthalein at 140–170 °C. Synthesis using microwave heating has also been attempted. This one-pot synthesis of sulfonephthaleins via the in situ prepared *o*-sulfobenzoic anhydride has several advantages, such as enhancement in yield, simplification, reduced reaction and processing time, and solvent-free condition.

RESULTS AND DISCUSSION

The synthesis of phenolsulfonephthalein from saccharin and phenol was carried out using different homogeneous and heterogeneous catalysts. The results are presented in Table 1.

As can be seen from the results, the greatest yield of phenol sulfonephthalein was obtained when 1 mmol of saccharin and 3 equivalents of concentrated H_2SO_4 (98%) were heated with 2.2 mmol of phenol at 140 °C for 3.5 h. The product was identified as phenol red by direct comparison with the commercial sample. All the spectral and analytical data measured by high-performance liquid chromatography (HPLC) of our product were in full agreement with the commercial sample of phenol red. Elemental analysis showed absence of nitrogen, thus ruling out the formation of phenolsulfonephthalein **2** (Scheme 1). These results reveal that saccharin is most probably hydrolyzed to form 2-sulfobenzoic anhydride (**3**, Scheme 1) with the elimination of ammonia in the form of ammonium sulfate, and the resulting 2-sulfobenzoic anhydride is reacted with phenol to form phenol red. To confirm this assumption, saccharin was heated with concentrated H_2SO_4 at 140 °C for 3 h. After cooling the reaction mixture and the usual workup, a colorless crystalline product was obtained. It was characterized with the help of NMR and mass spectroscopy as 2-sulfobenzoic anhydride **3** (mp 121 °C, lit. mp[3] 120 °C). 2-Sulfobenzoic anhydride: ^{1}H NMR (DMSO $d_6 + CDCl_3$): δ 8.10–8.33 (m, 4H, ArH), LCMS: 184 (M^+), 120, 104, 92, 76 (100), 64. The elemental analysis of **3** showed the absence of nitrogen. Also, when saccharin was heated with 20% oleum at 140 °C for 3 h, 2-sulfobenzoic anhydride **3** was obtained after the usual workup. No phenolsulfonephthalein was formed in the reaction when H_2SO_4 was replaced by HCl or solid acid, such as $ZnCl_2$, EPZ, Hβ zeolite, or Dowex-50 (Table 1).

Table 1. Synthesis of phenlosulfonephthalein from saccharin and phenol under different reaction conditions

Expt.	Saccharin (mmol)	Phenol (mmol)	Reagent/catalyst	Temp. (°C)	Time (h)	Yield[a] (%)
1	1	3	H_2SO_4 (3 eq.)	140	3.5	26
2	1	3	Oleum (3 eq.)	140	3.5	4
3	1	2	H_2SO_4 (2 eq.)	140	3.5	18
4	1	3	H_2SO_4 (3 eq.)	100	5	5
5	1	2.2	H_2SO_4 (3 eq.)	140	3.5	27
6	1	3	HCl (3 eq.)	140	3.5	0.0
7	1	3	$ZnCl_2$ (10%)/EPZ-10 (20%)	160	10	0.0
8	1	3	Hβ/Dowex-50 (20%)	140	5	0.0

[a]Yields indicated here are isolated yields. Phenol red is water soluble and could not be fully recovered after workup.

Different sulfonephthaleins were synthesized from saccharin and different substituted phenols, using concentrated H_2SO_4 (3 eq.); the results are presented in Table 2. All the products were identified by spectral analysis. *o*-Cresol, *m*-cresol, xylenol, and aminophenol had red, purple, blue, and purple colors respectively.

Table 2. Synthesis of different phenolsulfonephthaleins [reaction mixture = saccharin (1 mmol) + substituted phenol (2.2 mmol) + conc. H_2SO_4 (3 eq.)]

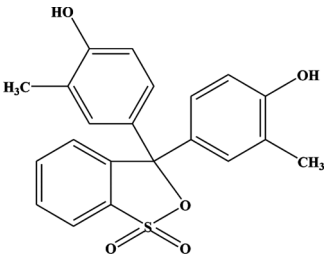
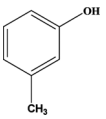
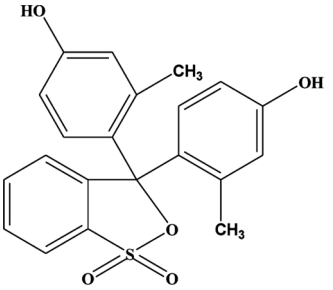
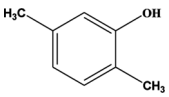
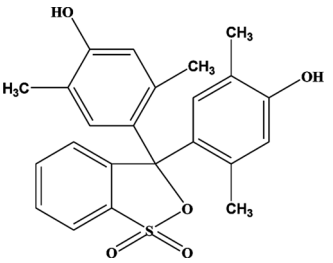
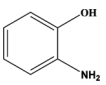
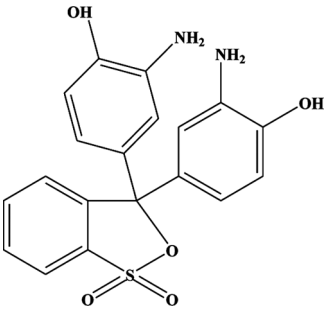
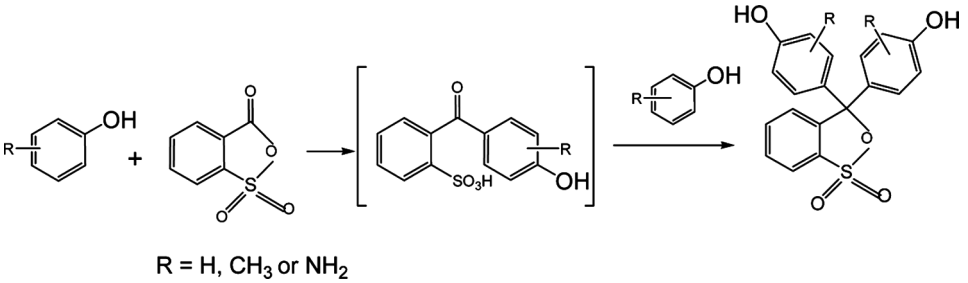
Expt.	Substituted phenol	Temp. (°C)	Time (h)	Product	Yield (%)
1		140	4		33
2		110	4		34
3		110	4		18
4		140	4		21
5	-do-	170	2	-do-	22

Table 3. Microwave synthesis of phenolsulfonephthalein from saccharin and phenol

Expt.	Saccharin	Phenol	Catalyst	Time (s)	Yield (%)
1	1 (equiv.)	0.5 (equiv.)	H_2SO_4 (3eq)	36	10
2	1 (equiv.)	2.2 (equiv.)	H_2SO_4 (3eq)	36	21
3	1 (equiv.)	3 (equiv.)	H_2SO_4 (3eq)	36	22
4	1 (equiv.)	2.2 (equiv.)	A[a]	120	No reaction
5	1 (equiv.)	nil	H_2SO_4 drops	120	93 (2-sulfobenzoic anhydride)

[a]BF_3 etherate, Dowex-50, Amberlyst-15, HCl, Hβ zeolite, HY zeolite, or $ZnCl_2$.



Scheme 2. Plausible mechanism for formation of sulfonephthalein from sulfobenzoic anhydride and phenol.

Microwave-mediated condensation of saccharin with phenol was also attempted to improve the product yield (Table 3). Other acidic reagents such as BF_3-etherate, Dowex-50, Amberlyst-15, HCl, Hβ zeolite, HY zeolite, and $ZnCl_2$ were tried instead of H_2SO_4. However, only the concentrated sulfuric acid or oleum was found to give the desired result (Table 3). A good yield of phenolsulfonephthalein was obtained by irradiating 1 equivalent of saccharin with 2.2 equivalents of phenol and 3 equivalents of H_2SO_4 in a domestic microwave for 36 s. The microwave-assisted synthesis of substituted phenolsulfonephthaleins was also attempted, but the results obtained were not consistent, most probably because of the lack of temperature control in the domestic microwave oven.

The formation of sulfonephthalein from substituted phenol and *o*-sulfobenzoic anhydride has been extensively studied. The formation of the sulfonephthalein takes place in two stages (Scheme 2). First, a molecule of anhydride combines with a molecule of substituted phenol to form addition compound, a tautomeric substance (an intermediate acid). The intermediate acid then reacts with 1 mol of phenol to give the corresponding sulfonephthalein.

EXPERIMENTAL

Synthesis of 3,3-Bis(4-hydroxybenzoxathiole-1,1-dioxide (Phenol Red) (Table 1, Entry 5)

Saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added to a three-necked, round-bottomed flask provided with magnetic needle, water condenser, and $CaCl_2$

guard tube. The reaction mixture was heated to 140 °C for 1 h, and 2.2 mmol phenol was added to it. The reaction mixture was then heated under stirring at 140 °C for 4 h. After completion of the reaction (TLC), the reaction mixture was poured into ice water, and steam distillation was carried out to remove phenol. The crude product was washed with benzene and diethyl ether to remove saccharin. The residue was then dissolved in hot sodium carbonate solution and filtered, and filtrate acidified was with diluted HCl. The precipitated colored solid product was filtered, dried, and purified by column chromatography on silica gel.

Synthesis of Sulfonephthaleins in Microwave

In a thick glass vial, saccharin and phenol in 1:2.2 ratio were added. This was followed by an addition of concentrated H_2SO_4. The vial was kept in a beaker and heated in the microwave oven (720 W) for 36 s to 5 min. The colored product was cooled and subjected to purification as described earlier.

Preparation of 2-Sulfobenzoic Anhydride

(1) A mixture of saccharin (100 mg) and concentrated H_2SO_4 (3 drops) was heated at 140 °C for 3 h in an oil bath. On cooling, a colorless crystalline solid product was obtained; it showed a sharp melting point at 121 °C.
(2) In a thick glass vial, saccharin (100 mg) and concentrated H_2SO_4 (3 drops) were added, and the mixture was heated in the microwave oven for 32 s. A clear colorless solution was obtained, which on standing became a crystalline solid product [yield 95 mg (95%), mp 121 °C].

The same reaction, when carried out by using oleum (3 drops) for 47 s, yielded 93 mg (93%) of the product.

In conclusion, the synthesis of different phenolsulfonephthaleins was achieved in one pot from saccharin and phenol or substituted phenol via the in situ formation of 2-sulfobenzoic anhydride. The synthesis from saccharin instead of the expensive sulfobenzoic anhydride, use of H_2SO_4 as condensing agent, and solvent-free reaction make this method more economical and environmentally benign.

Spectroscopic Data

3,3-Bis(4-hydroxybenzoxathiole-1,1-dioxide (phenol red) (Table 1, Entry 5). Mp: >300 °C; IR (nujol): 1583.94, 1553.83, 1460.01, 1366.04 cm^{-1}; ^1H NMR: δ 7.52 (d, $J = 8$ Hz, 4H), 7.83 (dd, J = 8 Hz, 8H), (DMSO-d_6 + $CDCl_3$): 8.08–8.63 (m, 4H); ^{13}C NMR (200 MHz): δ 156.99, 139.84, 131.87, 130.20, 128.55, 127.57, 113.65, 9928, 93.88.

3,3-Bis(4-hydroxy-2-methylphenyl)-3*H*-2,1λ^6-benzoxathiole-1,1-dioxide (*o*-cresol red) (Table 2, Entry 1). Mp: 295 °C; IR (nujol): 2924.68, 2854.74, 1625.01, 1459.4 cm^{-1}; ^1H NMR (200 MHz) (DMSO-d_6 + $CDCl_3$: δ 1.34 (s, 6H), 5.87 (d, $J = 6$ Hz, 2H), 6.34–6.41 (m, 4H), 6.70–6.76 (m, 2H), 7.34 $J = 6$ Hz, 2H); ^{13}C NMR (200 MHz): δ 168.48, 152.83, 141.63, 136.66, 134.10, 133.54, 128.10, 125.80, 117.74, 77.20, 14.88; LCMS: 405.0 (M^+ + Na), 383.1 (M^+ + 1).

3,3-Bis(4-hydroxy-3-methylphenyl)-3H-2,1,λ^6-benzoxathiole-1,1-dioxide (*m*-cresol purple) (Table 2, Entry 2). Mp: 296 °C; IR (nujol): 2927.47, 2855.46, 1603, 1455.75, 1215.76, 757.18, 669.01 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 1.05 (s, 6H), 6.10–6.13 (m, 2H), 6.75–6.81 (m, 4H), 6.93 (d, $J = 6$ Hz, 1H), 7.00–7.10 (m, 2H), 7.35 (d, $J = 6$ Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d_6 + $CDCl_3$): δ 167.89, 154.79, 142.62, 138.68, 136.24, 133.83, 133.46, 127.82, 127.12, 119.85, 117.93, 77.43, 14.59; LCMS: 405.2 ($M^+ + Na$), 383.3 ($M^+ + 1$).

3,3-Bis(4-hydroxy-2,5-dimethylphenyl)-3H-2,1λ^6-benzoxathiole-1,1-dioxide (*p*-xylenol blue) (Table 2, Entry 3). Mp: 215 °C; IR (nujol): 3369.60, 2924.39, 2855.01, 1628.77, 1460.51, 1256.86, 761.76, 659.9 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 1.45 (s, 12H), 5.91–6.03 (m, 2H), 6.45–6.68 (m, 3H), 6.76–6.88 (m, 2H), 7.50–7.61 (m, 1H); ^{13}C NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 167.95, 154.37, 142.89, 138.37, 131.08, 128.03, 126.81, 126.35, 125.89, 77.46, 19.47, 13.70, LCMS (*m*/*e*): 411.2 ($M^+ + 1$), 433.1 ($M^+ + Na$).

3,3-Bis(2-amino-4-hydroxyphenyl)-3H-2,1λ^6-benzoxathiole-1,1-dioxide (Table 2, Entry 4). IR (nujol): 3566.52, 3373.62, 3020.10, 1644.30, 1451.66, 1258.28, 753.14, 606.21 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 6.85–6.92 (m, 6H), 6.99–7.02 (m, 2H), 7.03–7.05 (m, 2H); ^{13}C NMR (200 MHz, DMSO-d_6 + $CDCl_3$): δ 167.72, 143.08, 137.56, 132.43, 130.56, 130.13, 126.91, 124.40, 121.75, 118.05, 77.0, LCMS: 417.10 ($M^+ + 1$). (Mp: not determined).

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