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A facile synthesis of phthalein indicator dyes

Ram W. Sabnis *

Ascadia Inc., 1000 Westgate Avenue, St. Paul, MN 55114, USA

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ABSTRACT

The use of methanesulfonic acid offers a novel and highly efficient method for the synthesis of phthalein indicator dyes in excellent yields on an industrial scale.

Color change has been a fascination for individuals for a long time. Phthaleins acid–base indicators are traditionally used for color change.[1] Phthalein indicator dyes exhibit multi-applications[2] which include paints, adhesives, insecticides, soaps, and food storage. In addition, they are used in personal care products[3] such as cosmetics and diapers. Phthalein indicators show promising biomedical applications[4] in detecting viable cells, treating amyloid-associated diseases, genomics, blood analysis, urine analysis, and dental impression material.

The invention of phthalein indicators by Baeyer[5] has not only revolutionized the color chemistry, in general, but also has made a major breakthrough particularly involving the color-change concept. The use of phthalein indicators is wide spread; it has grown rapidly and has exploded in the past two decades. Generally, the phenol is condensed with phthalic anhydride in the presence of an acidic catalyst under anhydrous conditions. These catalysts include sulfuric acid, polyphosphoric acid, aluminum chloride, stannic chloride, and zinc chloride. Among the several methods reported using these catalysts,[6] most of these methods afforded tarry products with some by-products in poor yield. Even though several synthetic methods are reported[6] for phthalein indicators, only three indicators namely, phenolphthalein, *o*-cresolphthalein, and thymolphthalein are commercially available. The methods developed so far have limitations and drawbacks such as: The product is impure and the yield is low. These are the major reasons why the phthalein indicator chemistry has not moved beyond these three indicators on an industrial scale.

In continuation of our work on the development of useful synthetic methodologies[7] and novel dye chemistry,[8] we report here a facile, one-pot synthesis of phthalein indicator dyes using readily available and economical starting materials by a simple method. We have condensed 2 M equiv of a phenol or substituted-phenol **1** with 1 M equiv of a phthalic anhydride **2** in the presence of methanesulfonic acid under anhydrous condition. Methanesulfonic acid acts as a condensing agent as well as reaction medium. The carbon atom at the 4-position with respect to the aromatic hydroxyl group must not be substituted as it is necessary for the reaction. The actual condensation reaction was brought about by the action of heat, preferably in the presence of a dehydrating acid such as methanesulfonic acid. The reaction mixture was stirred and heated at 90 °C for 5 h. Care should be taken so that the temperature of the reaction does not exceed 100 °C, otherwise several by-products would be detected. The condensation of phenols with phthalic anhydride in the presence of methanesulfonic acid was fast but the ideal time for completion of the reaction is 5 h. The reaction mixture was then cooled to room temperature and slowly added to ice-water mixture when the product precipitated. The product was filtered, throughly washed with water, and dried. The crude products were purified by recrystallization from a suitable solvent with charcoal treatment-furnished pure phthalein dyes **3a**–**m**.[9] The crude products were dark brown to yellow in color. The color of the products after recrystallization (without charcoal treatment) was light brown to pale yellow. Thus, the charcoal treatment was necessary as it yielded phthalein dyes **3a–m** as white crystals. We have managed to substantially increase the

* Present address: Patent Law Department, Wyeth, 5 Giralda Farms, Madison, NJ 07940, USA. Tel.: +1 973 660 7674; fax: +1 973 660 7151.
E-mail address: ramsabnis@yahoo.com

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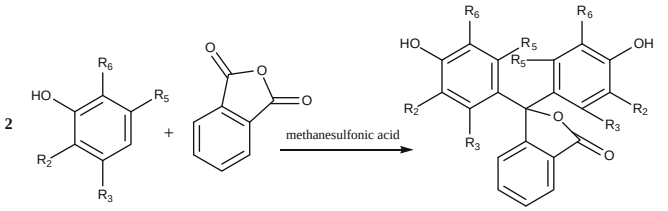
Table 1
A facile synthesis of phthalein indicator dyes **3a–m**



1 2 3

Entry	R_2	R_3	R_5	R_6	Product[a]	Yield (%)
1	H	H	H	H	**3a**	94
2	CH_3	H	H	H	**3b**	92
3	C_2H_5	H	H	H	**3c**	81
4	*iso*-Propyl	H	H	H	**3d**	83
5	*sec*-Butyl	H	H	H	**3e**	77
6	OCH_3	H	H	H	**3f**	79
7	C_6H_5	H	H	H	**3g**	94
8	CH_3	H	CH_3	H	**3h**	85
9	*iso*-Propyl	H	CH_3	H	**3i**	90
10	CH_3	H	H	CH_3	**3j**	91
11	OCH_3	H	H	OCH_3	**3k**	84
12	*iso*-Propyl	H	H	*iso*-Propyl	**3l**	89
13	CH_3	CH_3	H	CH_3	**3m**	73

[a] The reaction was conducted in anhydrous conditions.

yields (upto 73–94%) of the target phthalein dyes **3a–m**. Phthalein indicator dyes **3a–m** formed by this method are highly pure showing single spot on TLC (Thin Layer Chromatography) and no by-products were detected.

It is noteworthy that the starting materials and catalyst are readily available and highly economical. The reaction time is short (5 h) and work-up is easy. The products can be easily purified by recrystallization using charcoal treatment. The products are formed in excellent yields (Table 1). The phthalein compounds generated by this elegant method are pH indicators or acid–base indicators. They are colorless in acidic pH and deeply colored in alkaline pH. They exhibited red, pink, magenta, purple, violet, blue, and teal colors in basic pH. The color-change transition of phthalein indicator dyes is given in Table 2. This facile synthetic methodology can be applied to manufacture phthalein indicator dyes on an industrial scale in excellent yield and in high purity.

In conclusion, we have successfully developed an elegant, one-pot synthesis for phthalein indicator dyes using readily available and economical starting materials in the presence of methanesulfonic acid as a catalyst. The beauty of this method lies in the fact that the synthetic method offers short reaction time, ease of purification through crystallization, and high yields on an industrial scale. There is a huge scope to expand this approach for advancing color-change concept. Currently, we are investigating the synthesis of novel dye libraries, details of which will be published in due course. These dyes have potential applications in medical, coatings, and electronics field.

Table 2
Color-change transition of phthalein indicator dyes **3a–m**

Product	Color-change transition (pH: acidic to alkaline)
3a	Colorless to pink
3b	Colorless to red
3c	Colorless to magenta
3d	Colorless to pink
3e	Colorless to purple
3f	Colorless to violet-blue
3g	Colorless to purple
3h	Colorless to indigo-blue
3i	Colorless to blue
3j	Colorless to violet
3k	Colorless to teal
3l	Colorless to violet
3m	Colorless to teal

Acknowledgments

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References and notes

1. Sabnis, R. W. *Handbook of Acid–Base Indicators*; CRC Press: Boca Raton, 2008.
2. (a) Bramley, C. S. Eur. Pat. Appl. EP 1400574, 2004; *Chem. Abstr.* **2004**, *140*, 255055.; (b) Matsushima, A. Jpn. Kokai Tokkyo Koho JP 2003003149, 2003; *Chem. Abstr.* **2003**, *138*, 74331.; (c) Mohamed Mahgoub, H.; Ahmed Mahmoud Fahmy, A. PCT Int. Appl. WO 2002102150, 2002; *Chem. Abstr.* **2002**, *138*, 20926.; (d) Newkirk, R. S.; Gilmore, D. W. U.S. Pat. Appl. Publ. US 2006040835, 2006; *Chem. Abstr.* **2006**, *144*, 239248.; (e) Hoegl, L. Ger. Offen. DE 10021313, 2001; *Chem. Abstr.* **2001**, *135*, 343637.
3. (a) Dixit, D.; Pushpangadan, P.; Kochhar, V. K.; Kochhar, S.; Rao, C. V. PCT Int. Appl. WO 2005017134, 2005; *Chem. Abstr.* **2005**, *142*, 256737.; (b) Mody, N. U.S. Pat. Appl. Publ. US 2004191118, 2004; *Chem. Abstr.* **2004**, *141*, 301548.
4. (a) Mizutani, T.; Noda, N. Eur. Pat. Appl. EP 1624071, 2006; *Chem. Abstr.* **2006**, *144*, 187557.; (b) Gazit, E.; Porat, Y. PCT Int. Appl. WO 2005027901, 2005; *Chem. Abstr.* **2005**, *142*, 349074.; (c) Lerner, C. G.; Kakavas, S. J.; Wagner, C.; Chang, R. T.; Merta, P. J.; Ruan, X.; Metzger, R. E.; Beutel, B. A. *Antimicrob. Agents Chemother.* **2005**, *49*, 2767–2777.; (d) Blankenstein, G.; Peters, R. PCT Int. Appl. WO 2005119211, 2005; *Chem. Abstr.* **2005**, *144*, 33856.; (e) Lehmann, J. Ger. Offen. DE 4444533, 1996; *Chem. Abstr.* **1996**; *125*, 81239.; (f) Kamohara, H.; Watanabe, N.; Takeo, M.; Naito, H. U.S. Patent 6559200, 2003; *Chem. Abstr.* **2003**, *138*, 358529.
5. Baeyer, A. *Justus Liebigs Ann. Chem.* **1880**, *202*, 36–140.
6. (a) Ruminski, J. K. Pol. Patent PL 138940, 1988; *Chem. Abstr.* **1991**, *114*, 122040; (b) Parker, P. H. U.S. Patent 4652608, 1987; *Chem. Abstr.* **1987**, *107*, 78925; (c) Ruminski, J. K. *Chem. Ber.* **1983**, *116*, 970–979; (d) Prindle, H. B.; Ham, G. E. U.S. Patent 4252725, 1981; *Chem. Abstr.* **1981**, *94*, 208695.; (e) Hubacher, M. H. *J. Am. Chem. Soc.* **1942**, *64*, 2538–2539; (f) Cilianu, S.; Cilianu, S.; Ilie, C.; Visan, N.; Stefan, M. Rom. RO 91178, 1987; *Chem. Abstr.* **1988**, *108*, 112216.; (g) McKenna, J. F.; Sowa, F. J. *J. Am. Chem. Soc.* **1938**, *60*, 124–125; (h) Orndorff, W. R.; Murray, R. R. *J. Am. Chem. Soc.* **1917**, *39*, 679–697; (i) Gronowska, J. *Rocz. Chem.* **1959**, *33*, 191–195; *Chem. Abstr.* **1959**, *53*, 94608.; (j) Jaczewski, Z.; Karminski, W.; Kasprzyk, J.; Atamanczuk, B. *Przem. Chem.* **1982**, *61*, 93–95; *Chem. Abstr.* **1982**, *97*, 127423.; (k) Kasprzyk, J.; Wagner, A.; Karminski, W.; Jaczewski, Z.; Langier, G. Pol. PL 100343, 1979; *Chem. Abstr.* **1980**, *92*, 58604.; (l) Jaczewski, Z.; Karminski, W.; Kasprzyk, J.; Wagner, A. Pol. PL 112796, 1982; *Chem. Abstr.* **1982**, *97*, 215979.; (m) Borror, A. L. U.S. Patent 4001278, 1977; *Chem. Abstr.* **1977**, *86*, 108001.
7. (a) Rangnekar, D. W.; Kulkarni, V. S.; Ranade, P. V.; Sabnis, R. W. *Synth. Commun.* **2007**, *37*, 425–430; (b) Jachak, M. N.; Avhale, A. B.; Toche, R. B.; Sabnis, R. W. *J. Heterocycl. Chem.* **2007**, *44*, 343–347; (c) Toche, R. B.; Jachak, M. N.; Dalvi, T. S.; Sabnis, R. W.; Junek, H.; Kappe, T. *Org. Prep. Proced. Int.* **1998**, *30*, 367–372; (d) Sabnis, R. W.; Rangnekar, D. W. *J. Heterocycl. Chem.* **1992**, *29*, 1027–1029.
8. (a) Deligeorgiev, T. G.; Zaneva, D. A.; Kim, S. H.; Sabnis, R. W. *Dyes Pigm.* **1998**, *37*, 205–211; (b) Timcheva, I. I.; Maximova, V. A.; Deligeorgiev, T. G.; Gadjev, N. I.; Sabnis, R. W.; Ivanov, I. G. *FEBS Lett.* **1997**, *405*, 141–144; (c) Sabnis, R. W.; Deligeorgiev, T. G.; Jachak, M. N.; Dalvi, T. S. *Biotech. Histochem.* **1997**, *72*, 253–258; (d) Rangnekar, D. W.; Sabnis, R. W. *J. Chem. Technol. Biotechnol.* **1993**, *56*, 401–405; (e) Sabnis, R. W.; Rangnekar, D. W. *J. Heterocycl. Chem.* **1992**, *29*, 65–68; (f) Sabnis, R. W.; Kazemi, G.; Rangnekar, D. W. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3768–3770.
9. *General procedure*: A mixture of phenol **1** (0.133 mol) and phthalic anhydride **2** (0.074 mol) in methanesulfonic acid (0.416 mol) was stirred and heated at 90 °C for 5 h. The reaction mixture was cooled to room temperature and slowly added to ice-water when the product precipitated. The product was filtered, throughly washed with water, and dried. The crude product was purified by recrystallization from a suitable solvent with charcoal treatment-furnished pure phthalein dye **3**.
Compound **3a**: mp 261–263 °C (from methanol); FTIR (KBr): ν 3383, 3292, 2954, 1738, 1611, 1266 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.65 (s, 2H, 2OH), 6.79 (dd, 4H, aromatic), 7.10 (dd, 4H, aromatic), 7.64–7.91 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 318 (M^+). Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.47; H, 4.40. Found: C, 75.49; H, 4.44.
Compound **3b**: mp 221–223 °C (from ethanol); FTIR (KBr): ν 3463, 1739, 1714, 1612, 1276 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.58 (s, 2H, 2OH), 2.08 (s, 6H, $2CH_3$), 6.78–6.98 (m, 6H, aromatic), 7.63–7.89 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 346 (M^+). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.30; H, 5.20. Found: C, 76.27; H, 5.19.
Compound **3c**: mp 145–148 °C (from ethyl acetate/petroleum ether, 1:1); FTIR (KBr): ν 3389, 1783, 1718, 1605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.54 (s, 2H, 2OH), 2.43–2.50 (q, 4H, $2CH_2$), 1.00–1.05 (t, 6H, $2CH_3$), 6.74–6.96 (m, 6H, aromatic), 7.57–7.89 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 374

(M^+). Anal. Calcd for $C_{24}H_{22}O_4$: C, 77.00; H, 5.88. Found: C, 77.03; H, 5.86.

Compound **3d**: mp 158–159 °C (from methanol/water, 1:1); FTIR (KBr): ν 3383, 1733, 1608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.57 (s, 2H, 2OH), 1.05–1.07 (dd, 12H, $4CH_3$), 3.11–3.18 (sept., 2H, 2CH), 6.75–7.01 (m, 6H, aromatic), 7.59–7.90 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 402 (M^+). Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.46. Found: C, 77.62; H, 6.43.

Compound **3e**: mp 128–131 °C (from methanol); FTIR (KBr): ν 3400, 1722, 1607 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.50 (s, 2H, 2OH), 0.80 (t, 6H, $2CH_3$), 1.35–1.39 (p, 4H, $2CH_2$), 1.22 (d, 6H, $2CH_3$), 2.89–2.97 (sext., 2H, 2CH), 6.73–6.93 (m, 6H, aromatic), 7.59–7.90 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 430.5 (M^+). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.13; H, 6.97. Found: C, 78.17; H, 6.99.

Compound **3f**: mp 209–211 °C (from methanol); FTIR (KBr): ν 3517, 1747, 1701, 1279 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.27 (s, 2H, 2OH), 3.66 (s, 6H, $2OCH_3$), 6.65–6.78 (m, 6H, aromatic), 7.61–7.90 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 378 (M^+). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76. Found: C, 69.80; H, 4.72.

Compound **3g**: mp 238–240 °C (from methanol); FTIR (KBr): ν 3472, 1746, 1609 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.89 (s, 2H, 2OH), 6.97–7.18 (m, 6H, aromatic), 7.26–7.47 (m, 10H, aromatic), 7.63–7.92 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 470.5 (M^+). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.70; H, 4.68. Found: C, 81.74; H, 4.63.

Compound **3h**: mp 286–289 °C (from methanol); FTIR (KBr): ν 3393, 1729, 1611 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.40 (s, 2H, 2OH), 1.95 (s, 12H, $4CH_3$), 6.59–6.63 (m, 4H, aromatic), 7.46–7.91 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 374 (M^+). Anal. Calcd for $C_{24}H_{22}O_4$: C, 77.00; H, 5.88. Found: C, 77.05; H, 5.83.

Compound **3i**: mp 251–253 °C (from methanol); FTIR (KBr): ν 3382, 2961, 1736, 1687, 1290 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 2H, 2OH), 2.33 (s, 6H, $2CH_3$), 1.26–1.29 (dd, 12H, $4CH_3$), 3.14–3.27 (sept., 2H, 2CH), 6.34–6.79 (m, 4H, aromatic), 7.31–7.76 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 430.5 (M^+). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.13; H, 6.97. Found: C, 78.11; H, 6.94.

Compound **3j**: mp 247–249 °C (from methanol); FTIR (KBr): ν 3582, 3386, 1746, 1605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.45 (s, 2H, 2OH), 2.10 (s, 12H, $4CH_3$), 7.58–7.63 (m, 4H, aromatic), 7.78–7.87 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 374 (M^+). Anal. Calcd for $C_{24}H_{22}O_4$: C, 77.00; H, 5.88. Found: C, 77.03; H, 5.92.

Compound **3k**: mp 220–221 °C (from methanol); FTIR (KBr): ν 3388, 1769, 1606, 1369 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.71 (s, 2H, 2OH), 3.66 (s, 12H, $4OCH_3$), 7.65–7.68 (m, 4H, aromatic), 7.83–7.96 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 438 (M^+). Anal. Calcd for $C_{24}H_{22}O_8$: C, 65.75; H, 5.02. Found: C, 65.79; H, 5.07.

Compound **3l**: mp 212–214 °C (from methanol); FTIR (KBr): ν 3506, 1734, 1609 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.56 (s, 2H, 2OH), 1.02–1.05 (dd, 24H, $8CH_3$), 3.22–3.31 (sept., 4H, 4CH), 6.74–7.00 (m, 4H, aromatic), 7.59–7.92 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 486 (M^+). Anal. Calcd for $C_{32}H_{38}O_4$: C, 79.01; H, 7.81. Found: C, 79.06; H, 7.84.

Compound **3m**: mp 248–249 °C (from methanol); FTIR (KBr): ν 3510, 3390, 1746, 1609 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.44 (s, 2H, 2OH), 2.05 (s, 18H, $6CH_3$), 6.55 (s, 2H, aromatic), 7.46–7.90 (m, 4H, aromatic) ppm; Mass spectra (70 eV): m/z 402 (M^+). Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.46. Found: C, 77.64; H, 6.42.