



Synthesis, chemical reactivity, and photophysical properties of 2',7' phenylated rhodamine dyes



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ABSTRACT

While exploring water soluble rhodamine based fluorescent polymeric systems for biological imaging applications we came across new rhodamine derivatives that possess interesting optical properties. We report the synthesis of three different 2',7'-diphenylated rhodamine derivatives (**1–3**) with distinct photophysical properties. The three rhodamine derivatives differ by the number of methyl groups present on the nitrogens and their absorption maxima are red-shifted on increased methylation. We observed an unusual inertness of these compounds toward traditional DCC–DMAP esterification conditions, which we attribute to the ease of lactonization in the presence of even minute amounts of the nucleophile/base DMAP ($pK_a = 9.2$). Synthesis of acrylate esters was successfully accomplished using MSNT (1-(Mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole) coupling conditions using a much milder nucleophile/base, for example, *N*-methyl imidazole ($pK_a = 6.95$).

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Introduction

Rhodamine dyes belong to the fluorone dye family of compounds and are widely used as laser gain media as well as for contrast enhancement in biotechnological applications such as fluorescence microscopy, flow cytometry, fluorescence correlation spectroscopy, and enzyme-linked immunosorbent assay (ELISA).¹ Other uses include tracer dyes for fluorescent detection applications in groundwater flow tracing,² leak detection, septic, and sewer inspections and similar applications.³ The rhodamine family of dyes includes Rhodamine B, Rhodamine 6G, Rhodamine 123, Carboxytetramethylrhodamine (TAMRA), tetramethylrhodamine (TMR) and its isothiocyanate derivative (TRITC), sulforhodamine 101 (and its sulfonyl chloride form Texas Red), and Rhodamine Red and covers the spectral range from 450 to 650 nm emission with high quantum yields ranging from 0.65 to 0.95 depending on solvents and extinction coefficients of typically $\log \epsilon_{\max} > 8.8 \text{ M}^{-1} \text{ cm}^{-1}$.⁴

A further application area in which rhodamine dyes are commonly used is monitoring the residual levels of polymeric coagulants in wastewater effluents. A common approach to monitoring the level of water soluble polymer coagulants is to blend fluorescent dyes in small amounts and to use fluorescence of the mixture to determine the concentration of the polymer in aqueous systems.⁵ While exploring water soluble rhodamine based

fluorescent polymeric systems as tracer dyes and bio-imaging applications we discovered some interesting chemical and photophysical properties in the 2',7'-diphenylated rhodamine derivatives (**1–3**) in terms of their, (i) unusual ease of lactonization and therefore chemical inertness during DCC–DMAP esterification conditions; and (ii) changes in absorption and emission spectra based on the extent of methylation of the nitrogen groups.

Liu et al.,⁶ first reported the synthesis of tetramethyl derivative of the 2',7'-diphenylated rhodamine and used it as a benchmark system to compare the properties of the extended conjugation rhodamine based near-IR dyes they had synthesized and studied. We followed a similar synthesis protocol as described in Liu et al.⁶ for the synthesis of 2',7'-diphenylated rhodamine derivative **3**. However in addition to the tetramethyl derivative (**3**) we also observed the trimethyl- and dimethyl-diphenylrhodamine products (**2** and **1**, respectively) in reasonably larger yields compared to compound **3** under our synthesis conditions. All three compounds were easily purified using column chromatography and each of the products possessed interesting and distinct photophysical properties. We present here the five step synthesis procedure of 2',7'-diphenylated rhodamines, formation of three different 2',7'-diphenylated rhodamine products (*tetra*-, *tri*-, and *di*-methylated diphenylrhodamine) obtained during the condensation step, their photophysical properties and an exploration of their chemical inertness to DCC–DMAP (dicyclohexylcarbodiimide, dimethylaminopyridine) esterification conditions. Finally, we demonstrate an alternative esterification method using MSNT (1-(Mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole)⁷ which delivers high esterification yields.

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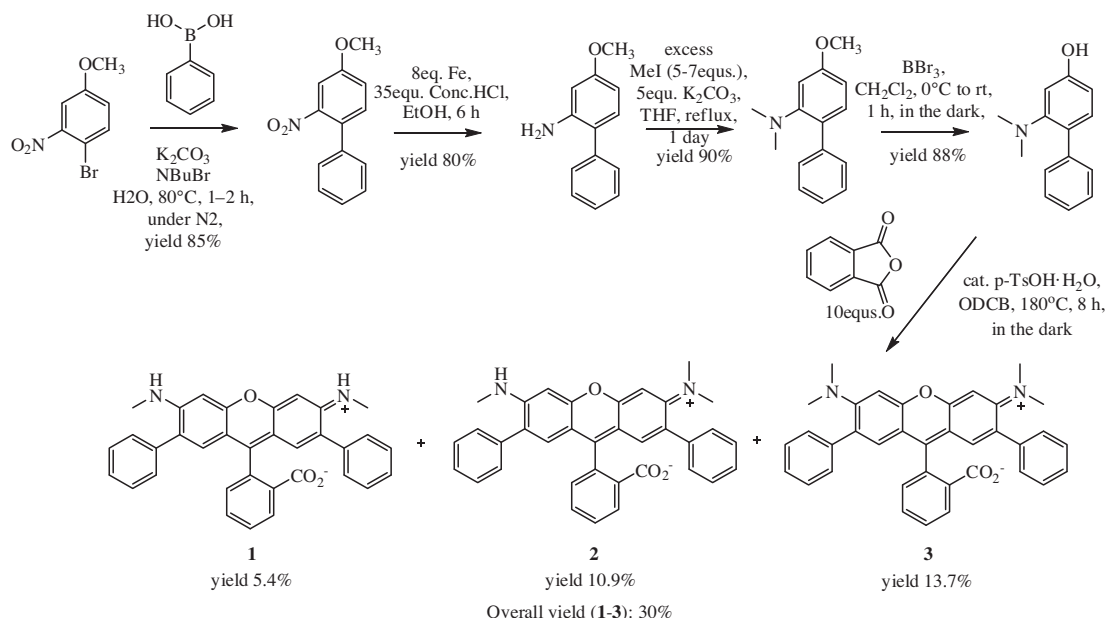
Results and discussion

The rhodamine derivatives (**1–3**) were prepared from commercially available 4-bromo-3-nitroanisole, as shown in Scheme 1. The first step involved the synthesis of the 4-methoxy-2-nitrophenyl via Suzuki coupling of 4-bromo-3-nitroanisole with the phenyl boronic acid and gave 85% yield.⁸ The second step was the reduction of the nitro-group to amine using conventional Fe/concentrated HCl which produced an 80% yield of the 4-methoxybiphenyl-2-amine. The third step was the methylation of the amino group using K_2CO_3 /MeI to obtain 4-methoxy-*N,N*-dimethylbiphenyl-2-amine in 90% yield. It is important to emphasize here that the excess MeI (5–7 equiv) was used and the reaction was monitored by TLC until the *N,N* dialkylation was complete. We observed that isolation of the product without base wash yielded the protonated form (yellow crystals) of the *N,N*-dimethylbiphenyl-2-amine due to HI by-product formation during the alkylation reaction. Therefore, after the reaction went to completion, the product was washed twice with $NaHCO_3$ to deprotonate the product, ultimately yielding *N,N*-dimethylbiphenyl-2-amine (yellow oil). By allowing the reaction to run to completion and isolating only the dialkylated product (based on 1H NMR analysis) we are confident that no monomethylated product was carried forward to the reaction with phthalic anhydride. The fourth step was the dealkylation of the methoxy group using BBr_3 to obtain 2-(dimethylamino)biphenyl-4-ol in 88% yield. After the reaction was complete, the product was washed thrice with $NaHCO_3$ to prevent isolation of the protonated form of the 2-(dimethylamino)biphenyl-4-ol. Finally, condensation of 2-(dimethylamino)biphenyl-4-ol with 10 equiv of phthalic anhydride, catalytic amount of *p*-toluenesulfonic acid, and heating at 180 °C for 8 h in dichlorobenzene gave a mixture of products (**1–3**) with an overall yield of 30% and individual yields of 5.4%, 10.9%, and 13.7%, respectively. In contrast to Liu et al.,⁶ which reports only the tetramethyl rhodamine (**3**) in 15% yield, we obtained three rhodamine derivatives (**1–3**) with overall yield of 30%. Due to the differing polarities of the *di*, *tri*, and *tetra*-methylated rhodamine derivatives, the products **1–3** eluted with different R_f values of 0.7, 0.5, and 0.2 in 2/8 Ethyl acetate/Hexane on silica gel TLC plate. The products were easily isolated in pure forms using silica gel chromatography and the same Ethyl

acetate/Hexane = 2:8 as elution solvent. The 1H NMR analysis confirmed the formation of three compounds **1–3**. It is interesting to note that the major difference between the three compounds is seen on the *N*-methyl groups in 1H NMR, one signal at 2.88 ppm (s, 6H's) for compound **1**, showing two signals for compound **2**, 2.6 ppm (s, 6H's), 2.87 ppm (s, 3H's), and only one signal at 2.6 ppm (s, 12H's) for compound **3**.⁹ LC-MS analysis of the compounds showed E^+ with molecular mass 512 (for compound **1**), 526 (for compound **2**), and 540 (for compound **3**) in the positive ion mode when eluted using a reverse phase C_{18} column with H_2O-CH_3CN solvent system.

The UV–vis absorption spectra of compounds **1–3** show that each molecule has a distinct absorption spectrum (in methanol) with the tetramethyl derivative (**3**) being the most red shifted λ_{max} at 578 nm (bathochromic shift) followed by compounds **2** and **1** which are 557 nm and 539 nm respectively. The trend in the shift of absorption spectrum we see here is very similar to the trend seen in the commercial molecules Rhodamine 6G (tetraethyl derivative) having λ_{max} in ethanol at 540 nm (533 nm in methanol) and Rhodamine B (dimethyl derivative) having λ_{max} at 526 nm in ethanol, respectively.¹⁰ We believe that the extended conjugation conferred by diphenylation of derivatives (**1–3**) is responsible for the red-shifts seen in their absorptions when compared to the non-phenylated versions. As shown in Figure 1, the absorption spectrum of Rhodamine 6G (tetraethyl derivative) has a similar absorption spectrum to the dimethyl diphenyl rhodamine derivative (**1**) and the tetramethyl diphenyl rhodamine derivative is red-shifted by ~18 nm. This shows that the phenylated rhodamine derivatives can effectively extend the spectral range of the rhodamine compounds to access longer wavelengths.

Next, we measured the fluorescence of compounds (**1–3**) and found that these compounds had distinct emission profiles and quantum yields. Specifically, increasing methylation correlated with decreases in quantum yield. Rhodamine 6G in methanol was used as a standard for relative quantum yield analysis,¹¹ each dye was diluted to the same peak absorbance (0.25 OD) and excited at their respective maximum absorbances (1 nm slit width). The acid form of the dimethyl, diphenyl derivative (**1**) exhibits an absolute quantum yield of >90% (comparable to Rhodamine 6G) as shown in Figure 1, while the trimethyl derivative (**2**)



Scheme 1. Synthesis route for 2',7'-diphenyl rhodamine derivatives (**1–3**).

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