



# An expedient synthesis of *N,N*-dialkylamino-dihydroxanthene-pyrylium conjugated near-infrared fluorescent dyes



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## ABSTRACT

An expedient synthesis of amino-(nor)dihydroxanthene-based fluorophores is reported, proceeding in two steps from commercially available salicylic aldehydes. The synthesis relies on the one-pot construction of the (nor)dihydroxanthene scaffolds through an oxa-Michael/retro-Michael/vinylogous aldol/dehydration cascade sequence. Further extension of the  $\pi$ -conjugated systems through a condensation reaction with a 2,4,6-trisubstituted pyrylium salt led to a novel class of near-infrared (NIR) fluorescent dyes with absorption/emission maxima in polar media in the ranges of 705–778 and 785–828 nm, respectively.

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## Introduction

The synthesis of near-infrared (NIR) absorbing/emitting small molecules<sup>1</sup> is of tremendous interest because of the increasing number of applications in optical bioimaging,<sup>2</sup> photoacoustic tomography<sup>3</sup> and, more broadly, in medical diagnostics<sup>4</sup> and theranostics.<sup>5</sup> NIR-emitting dyes offer important advantages in vivo in terms of sensitivity (e.g., deeper tissue penetration, low autofluorescence and background noise compared to the visible range), safety (e.g., noninvasiveness due to the lack of exposure to ionizing radiations), user-friendliness and affordable cost.<sup>6</sup> While the more widely used fluorophores<sup>7</sup> emitting in the therapeutic window (700–900 nm)<sup>8</sup> of the electromagnetic spectrum contain heptamethine cyanine (Cy7),<sup>9,10</sup>  $\pi$ -extended BODIPY and aza-BODIPY dyes,<sup>11,12</sup> we have noticed the recent emergence of modified xanthene-based fluorophores which, in our view, would beneficially complete the repertoire of NIR fluorescent dyes currently available. The dihydroxanthene scaffold was first reported by Grummt and Czerney<sup>13</sup> in 1996 and displayed an interesting emission above 730 nm. The initially developed chemistry was revisited in 2012 by Lin and co-workers who described analogs of rhodamine B which combined the stability of rhodamines (e.g., marked photo- and chemical-stability, especially under harsh conditions of pH

and temperature) and the easy modulation of their fluorescence properties through a spirocyclic/open-ring switching mechanism<sup>14</sup> with the far-emission usually observed for Cy7 dyes (Fig. 1A).<sup>15</sup> During the last few years, phenolic dihydroxanthene dyes have been extensively used in the design of reaction-based fluorescent probes for chemoselective bioimaging by taking advantage of their optically tunable hydroxyl group.<sup>16</sup> Conversely, less attention has been paid to the synthesis and bioanalytical applications of their *N,N*-dialkylamino counterparts.<sup>16h,17</sup> A cyanine-degradation-based approach was recently reported by Lin and co-workers<sup>18</sup> but a short, high yielding *de novo* access to the *N,N*-dialkylamino dihydroxanthene scaffold avoiding the destruction of valuable NIR cyanine dyes is desirable in order to provide more flexibility to access this promising fluorescent scaffold.<sup>19</sup>

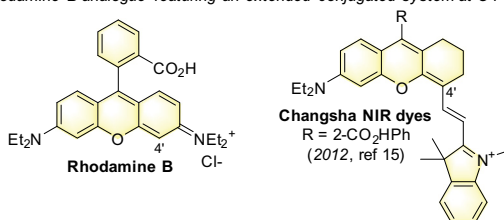
We have previously reported a streamlined synthesis of phenolic dihydroxanthene fluorophores thanks to the construction of the dye skeleton through an oxa-Michael/retro-Michael/vinylogous aldol/dehydration cascade sequence.<sup>20</sup> The newly developed *de novo* synthesis allowed access to phenolic near-infrared emitting dyes in three steps and paved the way for an expedient synthesis of fluorogenic probes derived from this ‘smart’ fluorescent phenol. We then wondered whether the modularity of this approach could be used to rapidly synthesize *N,N*-dialkylamino-dihydroxanthene dyes, aimed at assessing their photophysical properties in the NIR spectral range.

Herein, we report the convenient preparation of  $\pi$ -extended pyrylium-*N,N*-dialkylamino-dihydroxanthene chimera along with

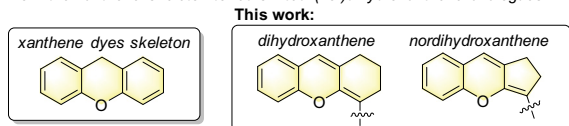
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E-mail address: [jean\\_alexandre@ices.a-star.edu.sg](mailto:jean_alexandre@ices.a-star.edu.sg) (J.-A. Richard).

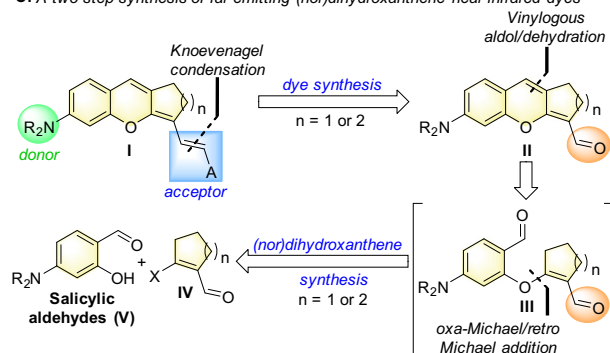
## A. Rhodamine B analogue featuring an extended conjugated system at C4'



## B. From the xanthene skeleton to red-shifted (nor)dihydroxanthene analogues



## C. A two-step synthesis of far-emitting (nor)dihydroxanthene near-infrared dyes



**Figure 1.** (A) Rhodamine B analog featuring an extended  $\pi$ -conjugated system; (B) (nor)dihydroxanthene scaffolds and (C) retrosynthetic analysis.

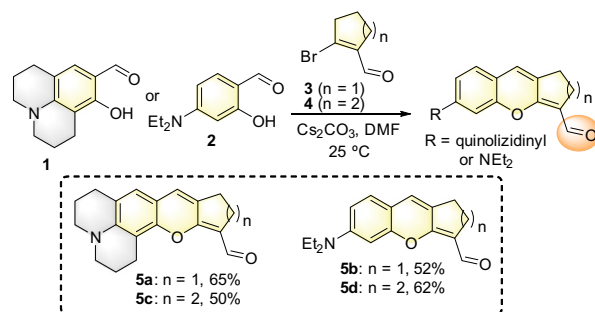
the previously unreported nordihydroxanthene scaffold (Fig. 1B). The spectral properties of these long-wavelength xanthene-like fluorophores were evaluated in polar media.

## Results and discussion

The desired *N,N*-dialkylamino (nor)dihydroxanthene dyes **I** featuring an electron acceptor moiety at one end of the  $\pi$ -conjugated system could be obtained by a Knoevenagel condensation of key intermediate aldehydes **II** (Fig. 1C). We hypothesized the latter would be derived from readily available starting materials salicylic aldehydes **V** and  $\beta$ -bromoaldehyde **IV** where the size of the ring could be varied in order to assess its effect on the fluorescence properties. Mechanistically, we previously proposed,<sup>20</sup> in the presence of base, salicylic aldehydes **V** would form a phenolate moiety that undergoes an oxa-Michael/retro Michael reaction leading to aryl ether **III**. Subsequent vinylogous aldol reaction followed by a final dehydration would close the central ring leading to the desired aldehyde **II** featuring the nordihydroxanthene ( $n = 1$ ) and dihydroxanthene ( $n = 2$ ) skeletons.

In order to test that hypothesis, we used commercially available 9-formyl-8-hydroxyjulolidine **1** and 4-(*N,N*-diethylamino)salicylaldehyde **2** as *ortho*-hydroxy benzaldehydes **V**, reacting with 5-membered and 6-membered  $\beta$ -bromoaldehydes **3** and **4**. Applying the optimized conditions previously found for the synthesis of the phenolic dihydroxanthene scaffold (3 equiv of Cs<sub>2</sub>CO<sub>3</sub> in DMF) we were pleased to observe that nordihydroxanthene aldehydes **5a** and **5b** could be isolated in 65% and 50% yield. Similar results were obtained using 6-membered-ring  $\beta$ -bromoaldehyde **4**, and aldehydes **5c** and **5d** were synthesized in 50% and 62% yield, respectively (Scheme 1).

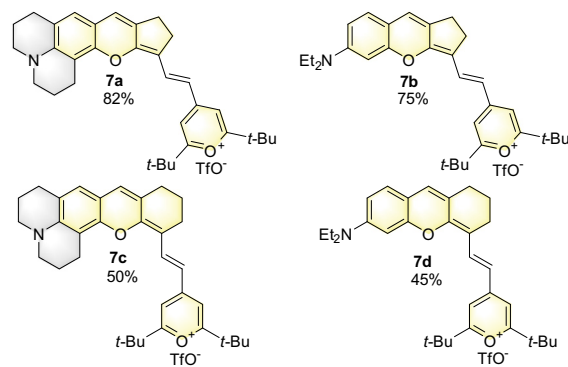
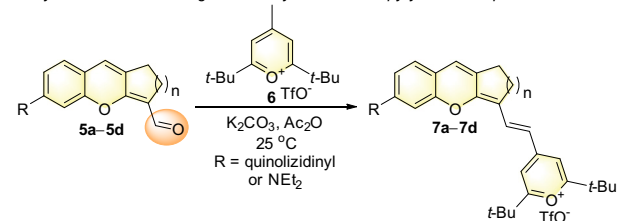
With these key intermediates in hand, the stage was set for their condensation to positively charged heterocycles bearing an



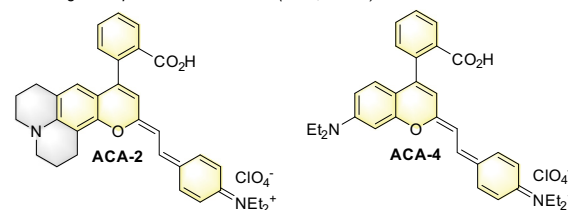
**Scheme 1.** Synthesis of (nor)dihydroxanthene aldehyde intermediates **5a–5d** through the oxa-Michael/retro-Michael/vinylogous aldol/dehydration cascade.

activated methyl aimed at extending their  $\pi$ -conjugated system and providing NIR fluorophores. Furthermore, the presence of a donor-acceptor pair (i.e., *N,N*-diethylamino and heteroonium) within the same molecular scaffold should promote internal charge transfer (ICT) and a dramatic red-shift in the absorption/emission maxima. Due to their valuable chemical reactivity and photophysical properties, pyrylium salts (including 4-methyl derivatives) are suitable synthetic building blocks for achieving this goal.<sup>22</sup> Thus, condensation of aldehydes **5a–5d** with commercial 2,6-di-*tert*-butyl-4-methylpyrylium triflate **6** in the presence of K<sub>2</sub>CO<sub>3</sub> in Ac<sub>2</sub>O at room temperature successfully provided dyes **7a–7d** with yields in the range 45–82% (Fig. 2A). The conversion of the aldehyde precursors **5a–5d** to the desired dyes appeared to be high by TLC, and we believed that the moderate isolated yields obtained

## A. Synthesis of far-emitting amino dihydroxanthene pyrylium fluorophores



## B. Far-emitting fluorophores from Lin et al. (2015, ref 23)



**Figure 2.** (A) Synthesis of *N,N*-dialkylamino (nor)dihydroxanthene pyrylium dyes **7a–7d** from aldehydes **5a–5d** and (B) known far-emitting fluorophores from Lin and co-workers.

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