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# A new iodine catalyzed regioselective synthesis of xanthene synthons ☆

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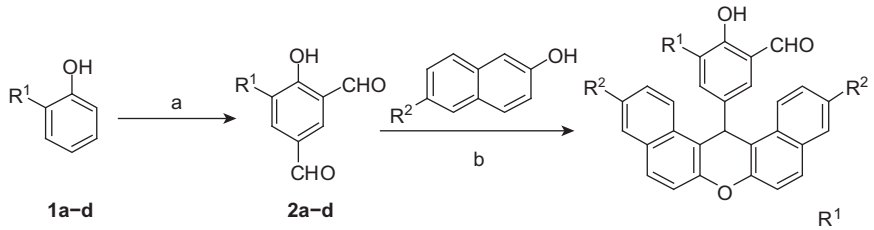
ABSTRACT

This Letter describes the iodine catalyzed one-pot regioselective synthesis of *p*-condensed xanthenes as our key point of transformation, which provides an efficient access to five skeletally diverse scaffolds in excellent yields.



Diversity-oriented synthesis (DOS) has received much attention lately as a tool for the exploration of the chemical space of molecular structures.[1–4] The aim of DOS is to obtain collections of small molecules as complex and diverse as possible. The screening of such molecular libraries, searching for perturbing effects on disease related biological pathways, may eventually lead to the identification of therapeutic protein targets, which can be modulated by small organic molecules. The development of effective strategies in DOS is therefore very important in finding new pharmacological targets.[5–11]




| | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **3a** | *sec*-Butyl | H | 90 |
| **3b** | *tert*-Buty | H | 87 |
| **3c** | iso-Propyl | H | 86 |
| **3d** | Ethyl | H | 85 |
| **3e** | *sec*-Butyl | Br | 82 |
| **3f** | *tert*-Buty | Br | 84 |
| **3g** | iso-Propyl | Br | 82 |
| **3h** | Ethyl | Br | 80 |

**Scheme 1.** Synthesis of regioselective xanthenes (**3a–h**). Reagents and conditions: (a) (1) hexamethylenetetramine/TFA, 120 °C, 3 h, (2) 10% $H_2SO_4$, 90–100 °C, 2 h; (b) $I_2$, 90–100 °C, 15 min.

☆ Part X in the series, 'Studies on Novel Synthetic Methodologies'.

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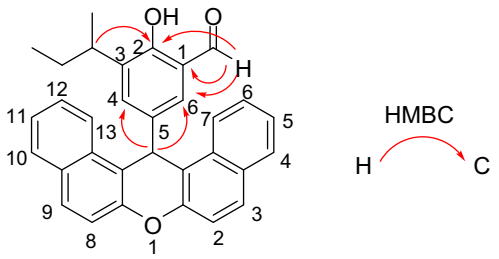


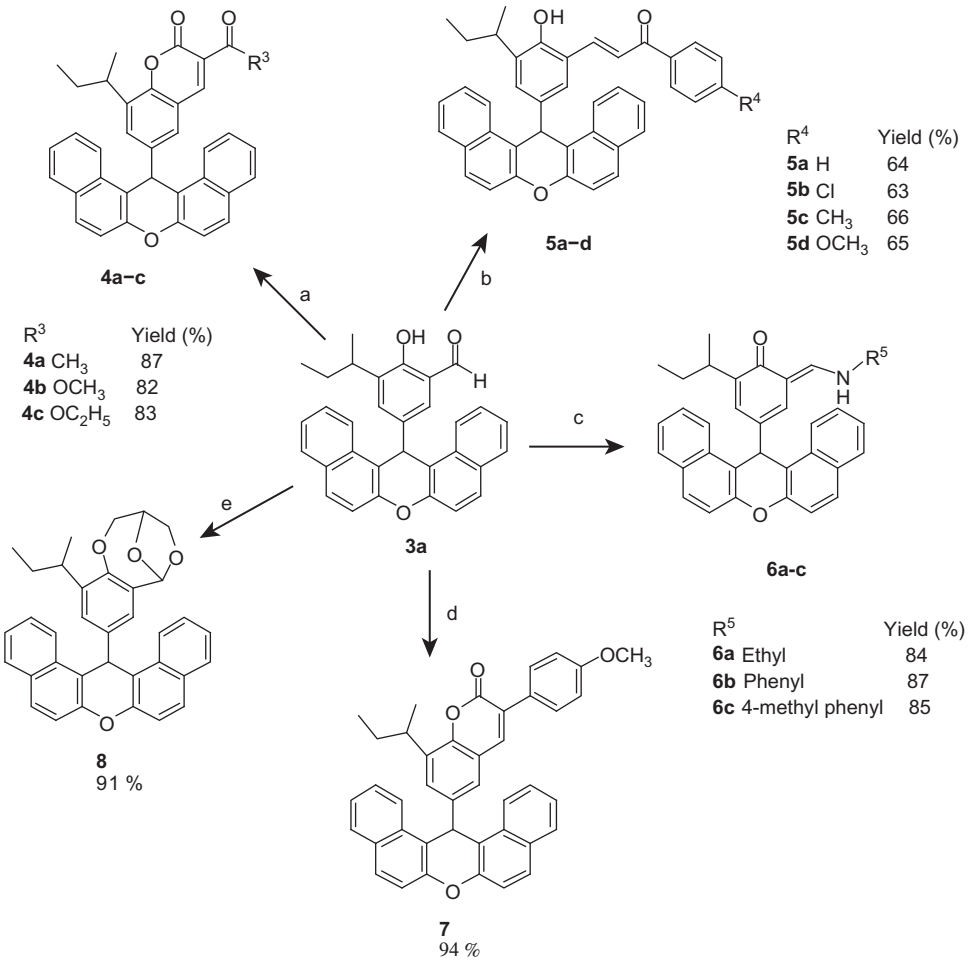

**Figure 1.** Selected $^{1}H$–$^{13}C$ HMBC correlations of compound **3a**.

Xanthenes are tricyclic dibenzopyrans with diverse pharmacological activities, such as antibacterials,[12] antivirals,[13] anti-inflammatories,[14] and find application even in photodynamic therapy.[15,16] Further, these compounds also have wide application in industries, such as dyes in laser technology[17] and for the fluorescent materials for visualization of biomolecules.[18] In addition many xanthene derivatives have shown anticancer activity.[19,20] However, the development of therapeutic agents that take advantage of this unique heterocyclic structure has been limited.

Considering the above valid points and our ongoing efforts on oxygenated heterocycles,[21] herein we report an efficient approach for regioselective synthesis of xanthenes and their further diversity oriented protocol for the synthesis of pharmaceutically important molecules like coumarins, chalcones, Schiff' base, arylcoumarins, and dioxocine analogs, using inexpensive starting materials.

The route followed for the preparation of regioselective xanthene and their further diversification are illustrated in Scheme 1. The Duff reaction on 2-*sec*-butylphenol (**1a**) gave compound 5-*sec*-butyl-4-hydroxyisophthalaldehyde (**2a**) which on condensation with β-naphthol in the presence of catalytic amounts of iodine[22] furnished *para*-selective dibenzoxanthenes (**3a**) exclusively in 90% yield. A likely explanation as to why the 5-*sec*-butyl-4-hydroxyisophthalaldehyde condenses so selectively with β-naphthol in the presence of iodine (mild lewis acid) is that, the reactive benzenoid forms are favored over the unreactive quinoid forms. Furthermore, the presence of the hydroxyl group α to the aldehyde will better stabilize (intramolecular H-bonding) the benzenoid rather than the quinoid form. Similar results were obtained, when other dialdehydes (**2a**–**d**) were condensed with β-naphthols to form their corresponding regioselective xanthenes (**3b–h**). To the best of our knowledge this is the first report of regioselective synthesis of xanthenes from aromatic dicarbaldehydes.

The structure elucidation of the versatile intermediate xanthene **3a** was done as follows. The ESI-mass spectrum gave a molecular ion at *m*/*z* 459 indicated the formation of the required product **3a**. In the IR spectrum of compound **3a** exhibited absorption band of carbonyl at 1639 $cm^{-1}$ and aromatic C–H stretch at 3057 $cm^{-1}$ indicating the presence of aromatic skeleton. The $^{1}H$ NMR spectrum of the product in addition to other signals showed signals




**Scheme 2.** Synthesis of substituted xanthenes of **3a**. Reagents and conditions: (a) $R^3COCH_2COOC_2H_5$, or $CH_2(COR^3)_2$, EtOH or MeOH, piperidine, reflux, 30 min; (b) 10% KOH, *p*-$R^4C_6H_4COCH_3$, EtOH, reflux, 4–5 h; (c) $R^5$-$NH_2$, PTSA, EtOH, reflux, 1 h; (d) *p*-$CH_3OC_6H_4CH_2COOH$, cyanuric chloride, *N*-methyl morpholine, DMF, 110 °C, 50 min; (e) epichlorohydrin, $Et_3N$, reflux, 75 min.

at $\delta$ 11.04 and 9.58 belonging to the hydroxyl and latter to a free aldehyde, respectively. The $^{13}$C NMR spectrum in addition to other signals, showed diagnostic signal at $\delta$ 196.9 (CHO) revealed that the product had aldehydic group. In the HMBC spectrum, C-2 ($\delta$ 158.0) gave correlations with protons present at $\delta$ 3.05, 7.23, 7.73, 11.04, and also at $\delta$ 9.58; this was only possible if the free aldehyde is at *ortho* position. This indicated that the condensation involved the aldehyde at *para* position (Scheme 1). Through HMBC we investigated further and found that proton at C-14 ($\delta$ 6.42) gave correlation with C-4 ($\delta$ 130.8), and C-6 (134.3). Finally, aldehydic proton ($\delta$ 9.58) gave correlation with C-1 ($\delta$ 120.5), C-2 ($\delta$ 158.0), and C-6 ($\delta$ 134.3). Thus, the final analysis with all the spectral data led to structure as **3a**. Selected HMBC correlations of compound **3a** are shown in Figure 1.

With an efficient route to the regioselective synthesis of xanthenes in hand, its diversification was undertaken to afford various analogs in a straightforward way in excellent yields (Scheme 2). Thus, subsequent diversification on **3a** was accomplished by applying the Knoevenagel condensation, catalyzed by piperidine, resulting in the formation of its coumarin derivatives (**4a**–**c**). Alternatively, compound **3a** on Claisen–Schmidt reaction[23] with different acetophenones in refluxing ethanol, in the presence of a 10% KOH furnished chalcones (**5a**–**d**). In all the chalcones synthesized the *trans* double bond (on the basis of coupling constant) was obtained exclusively. The low yields of chalcones obtained may be due to the combined effects of steric hindrance and the low reactivity of *ortho*-aldehyde which is involved in hydrogen bonding with the adjacent hydroxyl group. Furthermore, the compound **3a** on reaction with different amines in ethanol in the presence of catalytic amount of PTSA cleanly furnished its Schiff base (**6a**–**c**) derivatives that existed in keto-enamine form in high yields.[24] The formation of 3-arylcoumarin (**7**) was demonstrated by the reaction of **3a** with 4-methoxyphenylacetic acid in the presence of cyanuric chloride in excellent yield.[21b] Similarly, dioxocine (**8**) was derived by reaction of **3a** with epichlorohydrin using triethylamine as catalyst.[21d] All compounds were characterized using $^1$H NMR, $^{13}$C NMR, 2D NMR, mass spectrometry, and IR spectroscopy. The purity of these compounds was ascertained by TLC and spectral analysis[25] (please refer to Supplementary data).

In summary, we describe a simple and efficient method for the synthesis of regioselective xanthene and their further diversification. The advantage of this method is the ease of modification of each unit and their combination with another pharmacophore as potential pharmacological agents. This transformation could be of immense importance to medicinal chemists using appropriate templates to generate an interesting library of substituted xanthenes.

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## Supplementary data

Supplementary data (Spectral data of all the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.061.

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25. Synthesis of 3-*sec*-butyl-5-(14*H*-dibenzo[*a*,*j*]xanthene-14-yl)-2-hydroxybenz aldehyde (**3a**): 5-*sec*-butyl-4-hydroxyisonaphthaldehyde (2 g, 9.708 mmol) and naphthalen-2-ol (2.796 g, 19.4 mmol) in the presence of iodine as catalyst, was heated at 90–95 °C for 15–30 min. The reaction was monitored by TLC to establish completion. The remaining $I_2$ was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by chloroform (3 × 50 mL). The combined organic layers were dried on $Na_2SO_4$, filtered, and concentrated to dryness under reduced pressure. The crude product was purified over column chromatography (100–200 mesh) to furnish compound **3a**. White solid, yield: 90%; mp 125–127 °C; IR (KBr): 3394, 3057, 1639, 1046 cm$^{-1}$; $^1$HNMR ($CDCl_3$, 300 MHz): $\delta$ 11.03 (s, 1H), 9.58 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 2H), 7.81–7.73 (m, 5H), 7.56–7.51 (m, 2H), 7.47–7.36 (m, 4H), 7.24–7.21 (m, 1H), 6.40 (s, 1H), 3.09–2.97 (m, 1H), 1.67–1.49 (m, 2H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.73 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 196.9, 158.0, 148.8, 136.7, 135.3, 134.3, 131.4, 131.3, 130.8, 129.2, 129.1, 126.9, 124.5, 122.6, 122.5, 120.5, 118.1, 116.9, 37.4, 32.9, 29.3, 20.2, 11.9; ESI-MS (*m*/*z*): 459 (M+H)$^+$. Anal. Calcd $C_{32}H_{26}O_3$: C, 83.82; H, 5.72. Found C, 83.96; H, 5.57.