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Convenient synthesis of 12*H*-benzo[*a*]xanthenes from 2-tetralone

Amitabh Jha* and Jennifer Beal

Department of Chemistry, Acadia University, Wolfville, NS, Canada B4P 2R6

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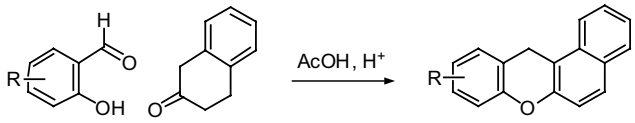
Abstract—Convenient and facile syntheses of 12*H*-benzo[*a*]xanthenes from 2-tetralone and 2-hydroxyaromatic aldehydes is described. 2-Tetralone reacted with 2-hydroxyarylaldehydes to yield 12*H*-benzo[*a*]xanthenes under acidic conditions.

Xanthenes and benzoxanthenes are important classes of compounds that find use as dyes, fluorescent materials for visualization of biomolecules and in laser technologies due to their useful spectroscopic properties.[1] Upon oxidation these compounds can be converted to corresponding xanthylium salts which are also useful as dyes and fluorescent materials.[2] Xanthene based compounds have also been investigated for agricultural bactericide activity,[3] photodynamic therapy,[4] anti-inflammatory effects,[5] antiviral activity[6] and for antagonism of the paralyzing action of zoxazolamine.[7]

A number of xanthene based compounds are also available from natural sources.[8] Santalin pigments, as they are popularly known, have been isolated from a number of plant species.[8]

Various literature procedures are available to synthesize xanthenes and benzoxanthenes, including palladium-catalyzed cyclization of polycyclic aryltriflate esters,[9] the intramolecular trapping of benzynes by phenols[10] and reaction of aryloxymagnesium halides with triethylorthoformate.[11] Additionally, 14*H*-dibenzo[*a*,*j*]xanthene (**8**) and analogues are prepared by condensation of 2-naphthol with aldehydes followed by dehydration,[12] with aldehyde acetals under acidic conditions,[12] with formamide,[13] with 2-naphthol-1-methanol,[14] and with carbon monoxide.[15]

We herein report a new, convenient and one-reaction step synthesis of 12*H*-benzo[*a*]xanthenes (**1–8**). This involves reacting 2-tetralone with substituted 2-hydroxyarylaldehydes and related compounds under acidic conditions and the yields are generally satisfactory (Scheme 1).



Scheme 1.

This work constitutes an extension of our previous results describing synthesis of 2-alkoxy-1-arylmethylnaphthalenes from 2-tetralone, aldehydes and alcohols[16,17] where reaction apparently followed aldehyde-active methylene condensation, vinyl ether formation followed by rearrangement leading to aromatization. On the same lines, it was envisioned that reactions between 2-tetralone and a compound with suitably placed aldehyde and hydroxy functions should produce O-containing polycyclic hydrocarbons. However, X-ray crystallography has shown that the geometry of the α,β-unsaturated system in 1-arylidene-2-tetralones (concomitant intermediates[17]) is *E*.[18] This configuration puts the hydroxyl group away from the carbonyl group of the first step condensation intermediate (**A**; Scheme 2) making the cyclization unlikely. After close examination, it was discerned that the presence of the extended conjugation should still make the cyclization reaction possible. To illustrate this, an example of the reaction between 2-tetralone and salicylaldehyde is depicted in Scheme 2.

Realizing this, reaction between 2-tetralone and 2-hydroxy-arylaldehydes were performed under acidic conditions[19] and as expected, 12*H*-benzo[*a*]xanthenes (**1–6**,

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* Corresponding author. Tel.: +1 902 585 1515; fax: +1 902 585 1114; e-mail: amitabh.jha@acadiau.ca

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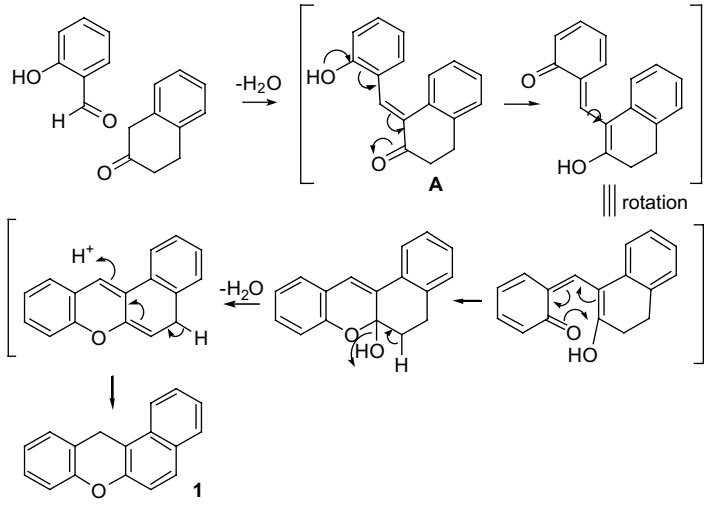
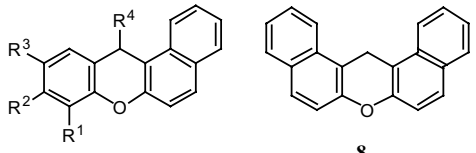


Scheme 2. Proposed mechanism of formation of compounds **1**–**8** illustrated for compound **1**.



1; $R^1=R^2=R^3=R^4=H$
2; $R^1=OCH_3$, $R^2=R^3=R^4=H$
3; $R^1=OC_2H_5$, $R^2=R^3=R^4=H$
4; $R^1=R^3=R^4=H$, $R^2=OH$
5; $R^1=R^3=R^4=H$, $R^2=OC_2H_5$
6; $R^1=R^3=R^4=H$, $R^2=OCH_2Ph$
7; $R^1=R^2=R^3=H$, $R^4=CH_3$

Figure 1. The structures of 12*H*-benzo[*a*]xanthenes **1**–**8**.

8, Fig. 1) were obtained in moderate to excellent yields. Attempts are being made to optimize the yields. Generally, the products were found to be stable but 12*H*-benzo[*a*]xanthen-9-ol (**4**) appeared to oxidize when exposed to atmosphere at room temperature; refrigeration in air-tight vessel alleviated this problem.

In order to verify whether these reactions are specific for aldehydes, one reaction was tried with 2-hydroxyacetophenone under similar conditions. This indeed yielded the desired 12-methyl-12*H*-benzo[*a*]xanthene (**7**) in 24% yield and unreacted 2-hydroxyacetophenone (~65%) was recovered; unreacted 2-tetralone apparently decomposed during the 3-day period. Compounds **2**–**7** are hitherto unknown in chemical literature. Table 1 indicates reaction time, yields and melting points of the products wherever possible.

In summary, we have devised a novel and convenient method to synthesize 12*H*-benzo[*a*]xanthenes from 2-tetralone and substituted salicylaldehydes and related compounds under acidic conditions. This transformation could be of immense importance to synthetic and combinatorial chemists using appropriate templates to generate an interesting library of substituted xanthenes.

Table 1. Compounds **1**–**8**

Product	Reaction time (h)	Yield (%)	Mp (°C)
1	16	71	92–93[a]
2	16	56	153–154
3	16	55	97–100
4	6	79	135–137
5	16	61	103–106
6	16	72	137–138
7	72	24	—
8	16	94	168–172[b]

All compounds were fully characterized by NMR, MS and HRMS analyses.
[a] Lit.[9] mp 89–90 °C.
[b] Lit.[5] mp 202 °C.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.046.

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19. In a typical procedure, the solution of appropriate 2-hydroxy aromatic aldehyde (5 mmol) in glacial acetic acid (8 mL) was cooled by an ice bath to ~0 °C. 2-Tetralone (5.05 mmol) was then added to it followed by addition of concd HCl and the contents were refrigerated for a varying amount of time. Progress of reaction was monitored by TLC using precoated fluorescent silica gel (10% EtOAc/hex) where formation of a new faster moving fluorescent spot was observed. Water (20 mL) was added to the reaction mixture and the solid obtained was triturated and filtered over suction. Solid product was purified using a silica gel (230–400 mesh) flash chromatography (30% CH_2Cl_2/hex). Compounds **4** and **8** were purified by digestion in MeOH. Data for a representative compound is presented here. Compound **4** 0.98 g (79% yield); mp 135–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (2H, t, J = 8.5 Hz), 7.75 (1H, d, J = 8.9 Hz), 7.60 (1H, t, J = 6.9 Hz), 7.47 (1H, t, J = 7.3 Hz), 7.27 (1H, d, J = 8.1 Hz), 7.20 (1H, d, J = 8.6 Hz), 6.61 (2H, d, J = 6.9 Hz), 4.87 (1H, s), 4.33 (2H, s); Long-range couplings in ^{1}H NMR of this compound, albeit expected, were not observed at 300 MHz; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.48, 152.07, 148.87, 132.48, 130.58 (for 2C), 128.86, 128.62, 127.10, 124.57, 122.70, 118.27, 112.28, 112.24, 111.12, 103.71, 24.58; IR (KBr) ν 3300, 1632, 1458, 1245, 1110, 816, 740 cm^{-1}. UV (MeOH, λ_{max}): 299, 321 and 334 nm; HRMS calcd for $C_{17}H_{12}O_2$: 248.0837; found: 248.0835; EIMS, 70 eV, *m*/*z* (% int.): 248 (M^+, 100), 247 (92), 124 (9).