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Efficient Ru^{III}-catalyzed synthesis of 9-aryl-9*H*-xanthene-3,6-diols as precursors to fluorones

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Abstract

Efficient condensation of resorcinol and various aromatic aldehydes in the presence of $RuCl_3 \cdot nH_2O$ as a homogeneous catalyst under reflux conditions was investigated. It was found that a very simple method afforded good to excellent yields of the desired products.

Keywords: Aldehyde; Resorcinol; Ruthenium; Xanthenediol; Fluorone

There has been tremendous interest to develop xanthene derivatives synthesis due to their biological activities such as antibacterial, antiviral and anti-inflammatory [1]. These heterocyclic compounds are also utilized as dyes [2]. Fluorone, fluorescein, rosamine and rhodamine are common xanthene dyes. Xanthene dyes are extracted from soil and plants such as *Indigofera longeracemosa* [3]. Daidzein and formonenetin which belong to the soy isoflavones, as bioactive compounds was obtained from resorcinol [4]. On the other hand, synthesis of fluorone derivatives has attracted considerable attention because they have found numerous applications [5–11]. Thermal and acid-catalyzed condensation of resorcinol with aldehydes and then oxidation of leuco base is one of the straightforward approaches for the synthesis of fluorone [12–16]. In this research we aimed at the synthesis of xanthenediols, which may be susceptible to further oxidation to fluorones.

Organic syntheses promoted by a catalyst, is our prime interest [17–19]. Recently, we have been involved in the study of the catalytic activity of ruthenium towards organic reactions such as oxidation of aromatic and heteroaromatic compounds [20], double-conjugate 1,4-addition to enones [21], nucleophilic addition to epoxides [22], Michael addition of indoles to hormone steroids [23], condensation of β-naphthol with aldehydes [24] and three-component cyclocondensation of β-naphthol, aldehydes, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) [25]. As a matter of fact, many organic transformations, which involve ruthenium species as catalyst, are known and well-documented [26,27].

Herein, we report a convenient method for the synthesis of 9-aryl-9*H*-xanthene-3,6-diols as precursors for fluorone dyes from condensation of resorcinol and aldehydes in the presence of $RuCl_3 \cdot nH_2O$ as a homogeneous catalyst (Scheme 1).

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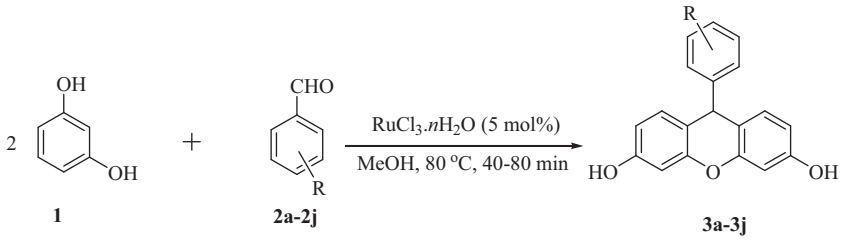


2a: R= H, **2b**: R= 4-NO_2, **2c**: R= 4-Cl, **2d**: R= 4-Br, **2e**: R= 4-OH, **2f**: R= 4-OCH_3, **2g**: R= 4-OH, 3-OCH_3, **2h**: R= 2-OH, 3-OCH_3, **2i**: 3,4-OCH_3, **2j**: R= 4-SCH_3

Scheme 1. Double condensation of resorcinol and aromatic aldehydes.

1. Experimental

All products were characterized by physical data (mp), spectral data (IR, ^{1}H NMR) and elemental analysis. Uncorrected melting points were measured by a BÜCHI melting point B-540 apparatus. IR spectra were carried out on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H NMR spectra were recorded at ambient probe temperature on a Bruker DRX-400 Avance spectrometer. Chemical shifts of ^{1}H NMR spectra were reported in ppm downfield from TMS as internal standard and coupling constants (*J*) were expressed in hertz. Thin layer chromatography (TLC) was performed on Silica gel 60 F plates eluting with petroleum ether–ethyl acetate, 10:3. Elemental analyses were performed on a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. Resorcinol, aldehydes, $RuCl_3{\cdot}nH_2O$ and solvents were purchased from Merck and used without further purification.

To a mixture of resorcinol (220.2 mg, 2 mmol) and benzaldehyde (106.1 mg, 1 mmol) in methanol (5 mL), $RuCl_3{\cdot}nH_2O$ (10.7 mg, 0.05 mmol) was added. The resulting mixture was then refluxed in an oil bath at 80 °C for 50 min. The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled at room temperature, the precipitate was filtered off and washed with cold methanol. The solid was dried under vacuum to afford the desired compound in pure form (261.3 mg, 90%). The same procedure was also used for the other products listed in Table 1.

1.1. 9-Phenyl-9H-xanthene-3,6-diol ***(3a)***

Solid; mp: 170–172 °C, IR (KBr): ν (cm^{-1}); 3380, 3010, 1615, 1520, 1490, 1420, 1280, 1080, 915, 835, 745; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ 7.21 (t, 2H, J = 7.6 Hz), 7.11 (t, 1H, J = 7.6 Hz), 7.04 (d, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 8.4 Hz), 6.41 (d, 2H, J = 8.4 Hz), 6.30 (s, 2H), 5.52 (s, 1H), 5.21 (s, 2H). Anal. calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.65; H, 4.87.

Supplementary data are also available for the other products listed in Table 1.

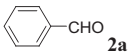
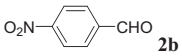
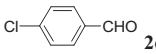
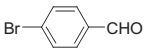
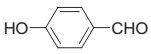
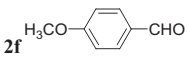
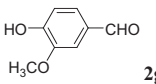
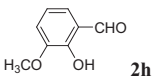
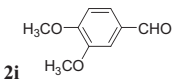
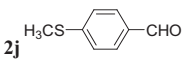
2. Results and discussion

Typical results for the ruthenium-catalyzed condensation of resorcinol with aromatic aldehydes are shown in Table 1 and indicate the scope of the reaction. In an optimized procedure (as it is outlined in Scheme 1), treatment of resorcinol (2 mmol) with benzaldehyde (1 mmol) in the presence of $RuCl_3{\cdot}nH_2O$ (5 mol%) in methanol (5 mL) at 80 °C for 50 min gave 9-phenyl-9*H*-xanthene-3,6-diol in 90% yield as a solid precipitate (Table 1, entry 1).

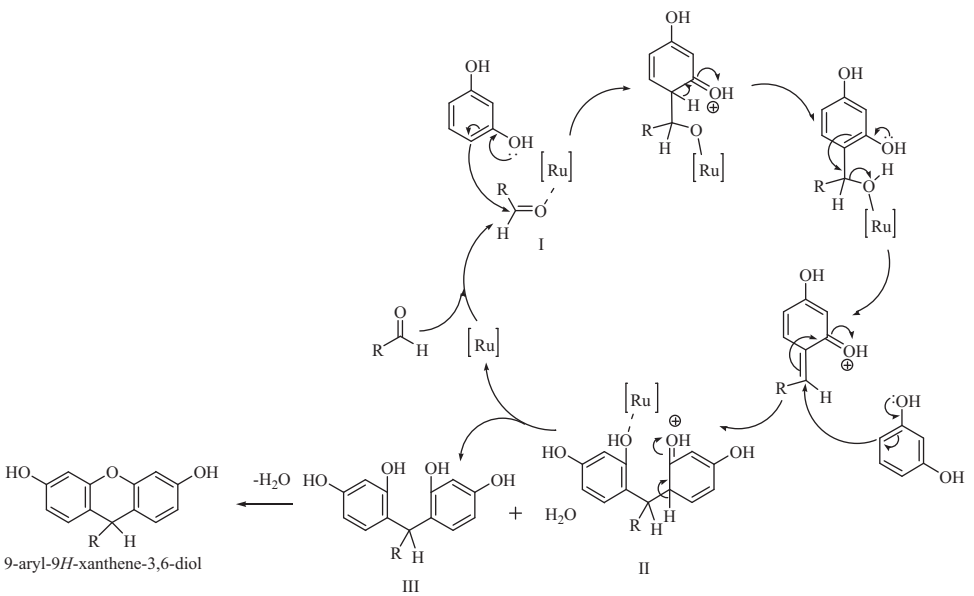
From the NMR spectral data, it was revealed that the reaction leads to the selective functionalization of resorcinol at C-6 rather than both at C-2 and C-6.

Various aromatic aldehydes bearing electron-withdrawing or electron-releasing groups were used and resulted in good to excellent yields of the desired products within 40–80 min (75–94%) without formation of any side products. It was shown that aromatic aldehydes with electron-withdrawing groups reacted faster than those bearing electron-donating groups and higher yields of product were obtained. The unique feature of the reaction is that corresponding 9-aryl-9*H*-xanthene-3,6-diol derivatives are insoluble in the reaction solvent and this leads to an easy workup (see Section 1). With regard to the aliphatic aldehydes, however, the present protocol resulted in trace yields of products.

Table 1
$RuCl_3{\cdot}nH_2O$ catalyzed synthesis of 9-aryl-9*H*-xanthene-3,6-diol derivatives.

Entry	Aldehyde	Time (min)	Product	Yield (%)[a]	Mp (°C)
1	 **2a**	50	**3a**	90	170–172
2	 **2b**	40	**3b**	92	316–318
3	 **2c**	45	**3c**	90	288–290
4	 **2d**	40	**3d**	94	310–312
5	 **2e**	60	**3e**	84	131–133
6	**2f** 	65	**3f**	84	200–202
7	 **2g**	70	**3g**	82	218–220
8	 **2h**	80	**3h**	75	214–216
9	 **2i**	65	**3i**	80	226–228
10	 **2j**	60	**3j**	84	206–208

Note: All products were characterized by ^{1}H NMR and IR data.
[a] Isolated yields.



Scheme 2. Plausible mechanism for the synthesis of 9-aryl-9*H*-xanthene-3,6-diol in the presence of $RuCl_3{\cdot}nH_2O$ as catalyst.

A plausible mechanism for this transformation under ruthenium catalysis is outlined in Scheme 2. As it is shown, prior activation of the carbonyl group of aldehyde by Ru^{III} to give (I) and then two successive nucleophilic attacks from two resorcinol molecules gives intermediate II. After loss of one molecule of water to give intermediate III, dehydration results in the desired product.

3. Conclusion

The present protocol provides a powerful and convenient method for the preparation of 9-aryl-9*H*-xanthene-3,6-diol derivatives. This method is endowed with several merits namely, simplicity in operation, mild reaction conditions, high yields of products and low catalyst loading.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2011.11.012.

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