

An efficient KHSO_4 catalyzed synthesis of xanthenes

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Abstract

KHSO_4 is an efficient catalyst for the condensation of β -naphthol, aromatic aldehydes, and 5,5-dimethyl-1,3-cyclohexanedione at 100°C to afford 9,9-dimethyl-12-phenyl-8,10,11,12-tetrahydro-9H-benzo[a]xanthen-11-one derivatives in 80–95% yields.

Keywords: aromatic aldehydes; 5,5-dimethyl-1,3-cyclohexanedione; KHSO_4 ; β -naphthol; xanthenes.

Introduction

Multicomponent reactions (MCRs) have attracted much attention due to their synthetic and practical efficiency, reduction of isolation and purification steps, minimization of costs, energy, time, and waste production (Anary-Abbasinejad and Saidipoor, 2008; Ghosh et al., 2008; Habibi et al., 2008). As a result, considerable efforts have been paid to the development of new and improved one-pot MCRs in recent years (Cui et al., 2006; Ghosh et al., 2007; Huang and Xue, 2007). In addition to this, the utility of MCRs is well represented in the synthesis of privileged medicinal scaffolds such as 1,4-dihydropyridines, dihydropyrimidines, decahydroquinolin-4-ones, and substituted indoles (Yadav et al., 2010). MCRs involve three or more substrates together reacting in a single vessel to form the desired product.

Xanthenes and benzoxanthenes are important intermediates in organic synthesis due to their wide range of biological properties such as antibacterial (El-Brashy et al., 2004), antiviral (Jamison et al., 1990), and anti-inflammatory activities (Chibale et al., 2003). Furthermore, these heterocycles display useful spectroscopic properties and are used as dyes in laser technologies and as fluorescent materials for the visualization of biomolecules (Wu et al., 2010). Several xanthene dyes are extracted naturally from soil and plants such as *Indigofera longeracemosa* (Licudine et al., 1997). Thus, the synthesis of benzoxanthene derivatives is currently of great interest.

Several synthetic methods for the preparation of xanthenes derivatives under solvent-free conditions in the presence of I_2 (Wang et al., 2009), $\text{NH}_2\text{SO}_3\text{H}$ (Heravi et al., 2010), $\text{HBF}_4\text{-SiO}_2$ (Zhang et al., 2009) have been reported. Xanthenes derivatives have also been synthesized using solvents and $\text{Sr}(\text{OTf})_2$ (Li et al., 2008), $\text{NaHSO}_4\text{-SiO}_2$ (Das et al., 2007), $\text{BF}_3\text{-OEt}_2$ (Sethukumar et al., 2011), prolitriflate (Li et al., 2010), and TBAF (Gao et al., 2009) as catalysts. Xanthenes have also been obtained in the presence of ionic liquid (Khurana and Magoo, 2009) and surfactant-combined catalyst (Shinde et al., 2011). However, in spite of their potential utility, many of these methods suffer drawbacks such as unsatisfactory product yields, expensive catalysts, and prolonged reaction times.

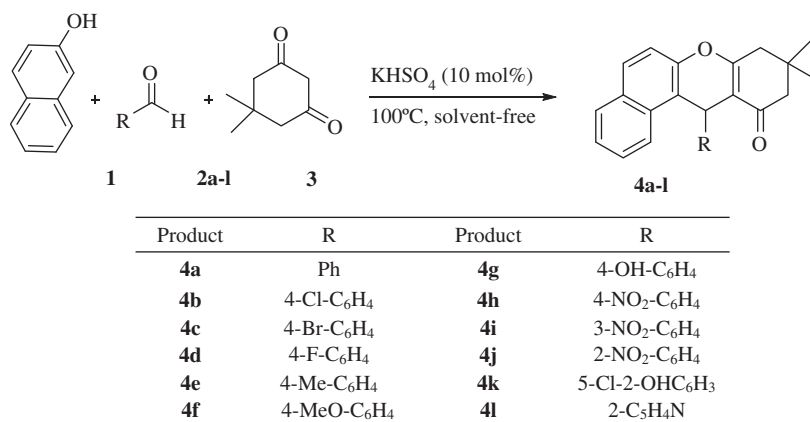
In continuation of our interest to develop efficient synthetic routes for biologically active compounds using green chemical techniques (Chandra Sekhar Reddy et al., 2010), we successfully used KHSO_4 as a catalyst instead of Lewis acids for the synthesis of xanthenes derivatives under a neat condition. This catalyst is inexpensive, mild, and does not require the maintenance of anhydrous conditions. There have been no reports on the synthesis of xanthenes derivatives using KHSO_4 as catalyst.

Results and discussion

A simple and an efficient procedure for the synthesis of 9,9-dimethyl-12-phenyl-8,10,11,12-tetrahydro-9H-benzo[a]xanthen-11-one derivatives **4** (Scheme 1) by condensation of aromatic aldehydes with β -naphthol and 5,5-dimethyl-1,3-cyclohexanedione in the presence of KHSO_4 under solvent-free conditions at 100°C is reported.

The reaction proceeds smoothly under these solvent-free conditions and gives the title compounds **4a–l** in 80–95% yields. The effect of various catalytic amounts of KHSO_4 on the synthesis of **4a–l** was examined and it was found that 10 mol% catalyst gave the maximum product yield.

The reusability of the catalyst is an important factor from an economical and environmental point of view and has been the focus of much attention in recent years. Thus, the reusability of KHSO_4 was studied in this system. The catalyst can easily be separated by dispersing the reaction mixture in ice water. In particular, it was found that the yield of **4b** decreased only slightly after the reuse of KHSO_4 for five times (Table 1). The yield of **4b** was 95%, 92%, 89%, 86%, and 85% for the first to fifth use of the same catalyst, respectively. To assess the efficiency and generality of this methodology, the synthesis of **4b** was compared with the previously reported methods (Das et al., 2007; Li et al., 2008; Khurana and Magoo, 2009; Nandi et al., 2009; Zhang et al., 2010; Shinde et al., 2011). It was found that the present method is superior to the reported



Scheme 1 Synthesis of xanthenes catalysed by KHSO₄.

methods with respect to reaction time, yield of the product, and amount of the catalyst.

Conclusion

A novel and highly efficient methodology for the synthesis of 9,9-dimethyl-12-phenyl-8,10,11,12-tetrahydro-9*H*-benzo[*a*]xanthen-11-one derivatives **4** by condensation reaction of aldehydes, β-naphthol and 5,5-dimethyl-1,3-cyclohexanedione in the presence of catalytic amounts of KHSO₄ (10 mol%) under solvent-free conditions is reported. The advantages of this method over other existing methods are reduced reaction times, higher yields, mild reaction condition, and easy work-up procedure.

Experimental

General

Infra red (IR) spectra were recorded on a Perkin-Elmer 683 spectrophotometer using KBr pellets. The nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ with tetramethyl silane (TMS) as reference on Bruker Avance 500 MHz spectrometer operating at 500 MHz for ¹H NMR and 125 MHz for ¹³C NMR. Mass spectra were recorded on a JEOL GC/MATE II GC-MS spectrometer. Elemental analyses were performed on Perkin-Elmer 2400 instrument. All chemicals were purchased from Sigma Aldrich and were used without further purification.

Typical experimental procedure

KHSO₄ (10 mol%) was added to a mixture of β-naphthol **1** (1 mmol), aldehyde **2** (1 mmol), and 5,5-dimethyl-1,3-

cyclohexanedione **3** (1 mmol) in a 50-mL flask. The mixture was heated and maintained at 100°C for 30 min. After completion of the reaction as indicated by thin layer chromatography (TLC), ice-water was added. The resultant solid was collected by filtration, washed with water, dried, and crystallized from ethanol. The physical and spectral data of the known compounds **4a–j** were in agreement with those reported in the literature (Das et al., 2007; Li et al., 2008; Foroughifar et al., 2009; Wang et al., 2009).

9,9-Dimethyl-12-phenyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-(12*H*)-one (4a) mp 148–150°C, lit. mp 149–150°C.

12-(4-Chlorophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4b) mp 188–189°C, lit. mp 188–189°C.

12-(4-Bromophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4c) mp 186–187°C, lit. mp 187–189°C.

12-(4-Fluorophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4d) mp 185–186°C, lit. mp 184–186°C.

9,9-Dimethyl-12-*p*-tolyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-(12*H*)-one (4e) mp 174–176°C, lit. mp 175–176°C.

12-(4-Methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4f) mp 205–207°C, lit. mp 207–208°C.

12-(4-Hydroxyphenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4g) mp 151–153°C, lit. mp 151–152°C.

12-(4-Nitrophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4h) mp 174–176°C, lit. mp 175–176°C.

12-(3-Nitrophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4i) mp 167–169°C, lit. mp 169–170°C.

12-(2-Nitrophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4j) mp 221–223°C, lit. mp 222–224°C.

12-(5-Chloro-2-hydroxyphenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (4k) Yield 86%; mp 263–265°C;

Table 1 Synthesis of **4b** using various amounts of KHSO₄.

Entry	KHSO ₄ (mol%)	Time (min)	Yield (%)
1	No catalyst	60	45
2	5	30	65
3	10	15	95
4	15	15	95

^1H NMR: δ 1.00 (s, 3H), 1.13 (s, 3H), 2.39 (s, 2H), 2.62 (s, 2H), 5.71 (s, 1H), 6.94–9.34 (m, 10H); ^{13}C NMR: δ 200.8, 167.4, 151.8, 147.9, 134.5, 131.7, 129.6, 128.5, 128.2, 127.7, 126.3, 125.5, 123.3, 120.5, 118.2, 116.8, 116.7, 113.5, 50.3, 41.6, 32.5, 29.1, 28.9, 28.2, 27.4; IR: ν 3300, 2950, 1630, 1575, 1370, 1210, 1175, 1030 cm^{-1} ; GC-MS: m/z (%) 404 (M^+ , 100). Anal. Calcd for $\text{C}_{25}\text{H}_{21}\text{ClO}_3$: C, 74.16; H, 5.23. Found: C, 77.01; H, 5.74.

9,9-Dimethyl-12-(pyridin-2-yl)-9,10-dihydro-8H-benzo[a]xanthene-11(12H)-one (4I) Yield 84%, mp 203–205°C; ^1H NMR: δ 0.99 (s, 3H), 1.10 (s, 3H), 2.26 (s, 2H), 2.55 (s, 2H), 5.62 (s, 1H), 6.55–8.05 (m, 10H); ^{13}C NMR: δ 197.6, 164.1, 149.4, 148.2, 133.8, 132.1, 132.0, 129.5, 128.9, 128.8, 127.4, 125.2, 124.3, 118.8, 117.5, 115.2, 112.9, 51.5, 41.9, 41.1, 34.1, 32.8, 29.7, 27.9; IR: ν 2950, 1670, 1630, 1545, 1350, 1220, 1150, 1025 cm^{-1} ; GC-MS: m/z (%) 355 (M^+ , 100). Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_2$: C, 81.10; H, 5.96. Found: C, 81.25; H, 6.10.

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