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Efficient Solvent Free Synthesis of 12-Aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones and 3*H*-Spiro[isobenzofuran-1,9'-xanthen]-3-one Derivatives Using Cobalt Hydrogensulfate as a Green, Heterogeneous and Reusable Catalyst

H. Eshghi*, M. Eftekhar, M. Rahimizadeh, M. Hassanpour and M. Bakavoli

Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran (Received 26 May 2015, Accepted 30 November 2015)

Cobalt hydrogensulfate is an efficient catalyst for the condensation of β -naphthol, aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione at 120 °C to afford 9,9-dimethyl-12-phenyl-8,10,11,12-tetrahydro-9-H-benzo[α]xanthen-11-one derivatives in high yields. Also, polycondensation reactions of phenols with phthalic anhydride were carried out in the presence of cobalt hydrogensulphate under solvent-free conditions. Simple and convenient procedure, high conversion, reusability of catalyst, easy purification and short reaction time are the advantageous features of this method.

Keywords: Cobalt hydrogensulfate, Heterogeneous and reusable catalyst, Xanthene derivatives, Solvent free

INTRODUCTION

Xanthenes and benzoxanthenes are an important class of biologically active heterocyclic compounds and drug intermediates [1]. Research on xanthenes, have attracted considerable interest in organic synthesis due to their wide range of biological and therapeutic properties such as antiviral [2] antibacterial [3] anti-inflammatory activities [4]. Among many xanthenes, fluoresceine compounds are known to have a high quantum yield of fluorescence in aqueous solution [5]. In addition, these compounds have been widely used as leco-dyes [6], laser technologies [7], photodynamic therapy [8] and as pHsensitive fluorescent materials for the visualization of biomolecules assemblies [9]. Several synthetic methods for the preparation of xanthenes derivatives have been reported such as I₂ [10], NH₂SO₃H [11], H₂SO₄ [12], tetradecyltrimethylammonium bromide (TTAB) [13], HClO₄-SiO₂ [14], Sr(OTf)₂ [15], HBF₄-SiO₂ [16], prolinetriflate [17], Fe(HSO₄)₃ [18], biodegradable ionic liquid [DDPA][HSO₄] [19]. Some of these procedures have some drawbacks, such as toxic solvents and

catalysts, long reaction times, undesirable yields and use of costly catalysts. Thus, there is a need for further development and designing an efficient, green and simple method for the preparation of xanthenes. Metal hydrogen sulfates have been used as an efficient catalyst in synthetic organic chemistry. A broad range of reactions including protection, deprotection, oxidation, C-C, C-N and C-O bond formation and cleavage took place in the presence of these reagents. In addition, stability, cheapness, efficiency and in many cases heterogeneous and reusability are other important advantages of these reagents [20-24]. In order to achieve a more efficient synthetic process, improving the yields and reaction times and also continuing our research on the application of acid-catalyzed reactions by Cobalt hydrogensulphate Co(HSO₄)₂ [25], we report a clean and environmentally friendly approach to the synthesis of 12-aryl-8,9,10,12tetrahydrobenzo[a]-xanthen-11-ones via multi-component reaction of aldehydes, 2-naphthol and dimedone and synthesis of 3H-spiro[isobenzofuran-1,9'-xanthen]-3-one derivatives by condensation of phenols with phthalic anhydride in the presence of Co(HSO₄)₂ as an heterogeneous catalyst under solvent-free conditions. Solvent-free reactions often lead to shorter reaction

^{*}Corresponding author. E-mail: heshghi@um.ac.ir Solvent-free reactions often lead to

times, increased yields, easier workup, and enhancing the regio- and stereoselectivity of reactions in green chemistry protocols [26-28].

EXPERIMENTAL

Materials and Instrumentation

All reagents were purchased from Merck Company and used without further purification. The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus. The FT-IR spectra were recorded on an Avatar 370 FT-IR Thermo Nicolet spectrometer. The mass spectra were recorded on a 5973 Network Mass Selective Detector. The ¹H and ¹³C NMR spectra were recorded on a Bruker AC 100 and Bruker DRX-400 Avance spectrometers at 400 and 100.65 MHz, respectively, using DMSO-d₆ or CDCl₃ as the deuterated solvents. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. Cobalt hydrogensulfate was prepared by our previously report [25].

General Procedure for Preparation of 12-Aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones Derivatives (1a-8a)

A 10 ml round-bottom flask was charged with the mixture of 2-naphthol (1 mmol), aryl aldehyde (1 mmol), dimedone (0.140 g, 1 mmol) and $Co(HSO_4)_2$ (0.1 mmol). The mixture was stirred at 120 °C for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to 25 °C, and the mixture was extracted with ethyl acetate (3 \times 10 ml). The cobalt hydrogen sulfate was filtered, washed with ethyl acetate, and oven-dried to be used again. The combined extracts were dried (MgSO₄) and the solvent was removed under reduced pressure to afford the crude product. The solid residue was recrystallized from aqueous ethanol to give the pure product.

General Procedure for Preparation of 3H-Spiro[isobenzofuran-1,9'-xanthen]-3-one (1b-6b)

A mixture of phenol (2 mmol), phthalic anhydride (1 mmol) and $Co(HSO_4)_2$ (0.3 mmol) was stirred at 120 °C

for appropriate time according to Table 2. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, methanol (5 ml) was added to the mixture and the resulting solution was filtered. Water (10 ml) was added to the filtrate and the mixture was extracted thoroughly with dichloromethane (3 \times 10 ml). The combined extracts were dried (Na₂SO₄) and the solvent was removed under reduced pressure to obtain the crude product. The residue was crystallized in ethanol to give pure 3H-spiro[isobenzofuran-1,9'-xanthen]-3-one derivatives.

Selected Spectroscopic Data

9,9-Dimethyl-12-(3-nitrophenyl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (4a). m.p.: 168-170 °C. IR (KBr, cm⁻¹): 3070, 2947, 1641, 1529, 1376, 1230, 1167, 1029, 803. ¹H NMR (CDCl₃, 400 MHz) δ: 1.22 (s, 6H), 2.21 (d, 1H), 2.25 (d, 1H), 2.32 (s, 2H), 5.40 (s, 1H), 7.35-7.45 (m, 4H), 7.51-7.55 (m, 2H), 7.85-7.90 (m, 3H), 8.22 (s, 1H). m/z, Calcd. for C₂₅H₂₁NO₄ [M]⁺: 399.15, found: 399.0.

12-(4-Methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**5a).** m.p.: 202-204 °C. IR (KBr, cm⁻¹): 3049, 2951, 1646, 1224, 1184, 1028. ¹H NMR (CDCl₃, 400 MHz) δ: 1.15 (s, 6H), 2.21 (d, 1H), 2.29 (d, 1H), 2.45 (s, 2H), 3.43 (s, 3H), 5.54 (s, 1H), 6.71 (d, 2H), 7.32-7.52 (m, 5H), 7.67-7.71 (m, 2H), 7.91 (d, 1H). m/z, Calcd. for $C_{26}H_{24}O_{3}[M]^{+}$: 384.17, found: 384.0.

3',6'-Dihydroxy-3H-spiro[isobenzofuran-1,9'- xanthen]-3-one (**1b**). m.p.: 314-316 °C. IR (KBr, cm⁻¹): 3400, 1645, 1620, 1470, 1275, 1250, 1220, 1120. 1 H NMR (CD₃COCD₃, 400 MHz) δ: 6.5-6.8 (m, 6H), 7.25 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.75 (m, 2H), 8.00 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 9.2 (b, 2H, D₂O exchangeable). m/z, Calcd. for C₂₀H₁₂O₅ [M]⁺: 332.07, found: 332.0.

3',4',5',6'-Tetrahydroxy-3H-spiro[isobenzofuran-1,9'-xanthen]-3-one (2b). m.p. > 300 °C. IR (KBr, cm⁻¹): 3400, 1625, 1465, 1210, 1165, 1120, 1100. ¹H NMR (CD₃COCD₃, 400 MHz) δ: 6.1 (d, 2H, J = 7.5 Hz), 6.6 (d, 2H, J = 7.5 Hz), 7.3 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.5-7.9 (m, 6H, 4H exchang), 7.9 (dd, 1H, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz). m/z, Calcd. for C₂₀H₁₂O₇ [M]⁺: 364.06, found: 364.0.

Table 1. Results of Aromatic Aldehyde Condensation with β-naphthol and 5,5-Dimethyl-1,3-cyclohexanedione in the Presence of Cobalt Hydrogensulfate

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.p. (°C)	Repoted	Ref.
1a	OH		25	90	149-151	148-150	[29]
2a	O H NO ₂	NO ₂	20	90	177-179	176-178	[29]
3a	CI	a contraction of the contraction	20	95	180-182	181-183	[29]
4 a	O ₂ N H	NO ₂	25	85	168-170	169-171	[29]
5a	O H OMe	OMe	40	80	202-204	202-204	[30]
6a	OH	OH	40	90	218-220	218-220	[31]
7a	O H Me	Me	30	90	175-176	176-177	[31]
8a	OHCI	CI	30	90	180-182	180-181	[31]

^aAll compounds were characterized on the basis of ¹H NMR and IR spectral data consistent with those of reported in literature.

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Table 2. Results of Polycondensation of Phthalic Anhydride and Phenols in the Presence of Cobalt Hydrogensulphate

Entry	Aldehyde	Product	Time (h)	Yield (%)	M.p. (°C)	Repoted	Ref.
1b	ОН	НО О ОН	0.5	80	314-316	312-315	[32]
2b	HOOH	НО ОН ОН	0.25	70	>300	>300	[32]
3b	OH Br	Br. O Br	14	65	277-278	276-277	[32]
4 b	OH	Cl	15	65	233-234	232-235	[32]
5b	OH OCH3	H ₃ CO OCH ₃	0.5	80	146-147	146-148	[32]
6b	OH	НОООН	1	75	258	258-262	[33]

^aAll compounds were characterized on the basis of ¹H NMR and IR spectral data consistent with those of reported in literature.

CHO
$$CO(HSO_4)_2$$
 $Co(HSO_4)_2$ Solvent-free, 120°C

Scheme 1. Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones derivatives

3',6'-Dibromo-3H-spiro[isobenzofuran-1,9'-

xanthen]-3-one (**3b).** m.p.: 277 °C. IR (KBr, cm⁻¹): 1750, 1600, 1465, 1250, 1105, 1060, 950. ¹H NMR (CDCl₃, 400 MHz) δ : 6.6 (d, 2H, J = 7.5 Hz), 7.15 (dd, 2H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.5 (d, 2H, J = 1.5 Hz), 7.7 (m, 2H), 8.05 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz). m/z, Calcd. for C₂₀H₁₀Br₂O₃ [M]⁺: 458.1, found: 458.0.

3',6'-Dichloro-3H-spiro[isobenzofuran-1,9'-

xanthen]-3-one (**4b**). m.p.: 233-234 °C. IR (KBr, cm⁻¹): 1765, 1635, 1475, 1260, 1095, 1075. ¹H NMR (DMSO,

400 MHz) δ : 6.9 (d, 2H, J = 8.5 Hz), 7.1-7.5 (m, 3H), 7.55 (d, 2H, J = 1.5 Hz), 7.75 (m, 2H), 8.05 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz). m/z, Calcd. for $C_{20}H_{10}Cl_2O_3$ [M]⁺: 368.00, found: 368.0.

3',6'-Dimethoxy-3H-spiro[isobenzofuran-1,9'-

xanthen]-3-one (**5b**). m.p.: 146-147 °C. IR (KBr, cm⁻¹): 1725, 1645, 1450, 1245, 1215, 1115, 1080. ¹H NMR (CD₃CN, 400 MHz) δ : 3.63 (s, 6H), 6.5-6.9 (m, 6H), 7.2 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.5-7.9 (m, 2H), 7.95 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz). m/z, Calcd. for $C_{22}H_{16}O_5$ [M]⁺: 360.1, found: 360.0.

Scheme 2. Synthesis of 3H-spiro[isobenzofuran-1,9'-xanthen]-3-one derivatives

Scheme 3. Synthesis of 3,3-bis(4-hydroxyphenyl)isobenzofuran-1(3H)-one

Scheme 4. Suggested mechanism of condensation reaction of aromatic aldehydes with β -naphthol and 5,5-dimethyl-1,3-cyclohexanedione in the presence of cobalt hydrogensulfate

Scheme 5. Suggested mechanism of condensation reaction of phthalic acid and phenols in the presence of cobalt hydrogensulfate

Table 3. Comparison of some other Methods with Cobalt Hydrogensulphate Catalyst for the Synthesis of 12-Aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-ones (**1a**)

Entry	Catalyst	Temp.	Time (min)	Yield (%)	Ref.
1	I_2	60	75	90	[34]
2	HClO ₄ /SiO ₂	80	72	89	[31]
3	Proline triflate	100	300	79	[17]
4	$Sr(OTf)_2$	80	300	85	[15]
5	PTSA	120	45	88	[35]
6	Co(HSO ₄) ₂	120	25	90	[a]

^aThis work.

Table 4. Comparison of some other Methods with Cobalt Hydrogensulphate Catalyst for the Synthesis of 3H-Spiro[isobenzofuran-1,9'-xanthen]-3-one Derivatives (**1b**)

Entry	Catalyst	Temp.	Time (h)	Yield (%)	Ref.
1	$ZnCl_2$	120-125	9	35	[36]
2	CH ₃ SO ₃ H	140	16	43	[32]
3	$CaCl_2$	200	a	43.37	[37]
4	$CaCl_2$	250	a	73.4	[37]
5	FeCl ₃	150	a	58.4	[37]
6	Co(HSO ₄) ₂	120	0.5	75	[b]

^aReaction times were not reported. ^bThis work.

3,3-Bis(4-hydroxyphenyl)isobenzofuran-1(3H)-one (6b). m.p.: 258 °C. IR (KBr, cm⁻¹): 3300, 1730, 1625, 1450, 1225, 1175, 1125. ¹H NMR (CD₃COCD₃, 400 MHz) δ : 6.8 (d, 4H, J = 8 Hz), 7.1 (d, 4H, J = 8 Hz), 7.55 (dd, 1H, J₁ = 7.5 Hz, J₂ = 1.5 Hz), 7.70 (dt, 1H, J₁ = 7.5 Hz, J₂ = 1.5 Hz), 7.8 (t, 1H, J = 7.5 Hz), 7.90 (dd, 1H, J₁ = 7.5 Hz, J₂ = 1.5 Hz), 8.65 (bs, 2H, D₂O exchangeable). m/z, Calcd. for C₂₀H₁₄O₄[M]⁺: 318.09, found: 318.0.

RESULTS AND DISCUSSION

A simple and an efficient procedure for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-ones derivatives (Scheme 1) were carried out on the one-pot multi-component reaction of aromatic aldehydes with β-naphthol and 5,5-dimethyl-1,3-cyclohexanedione in the presence of cobalt hydrogensulfate as a green, heterogeneous and reusable catalyst, under solvent-free conditions at 120 °C. The results are summarized in Table 1. Additionally, condensation of phthalic anhydride with phenols in the presence of cobalt hydrogensulfate under melt conditions gave fluorescein derivatives, (Scheme 2) and (Scheme 3). The corresponding desired products were isolated in excellent yields, as indicated in Table 2.

As expected, in the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones derivatives, electron-withdrawing groups on benzaldehyde accelerate the reaction rate in comparison to electron-donating groups which decrease the rate. Also in the synthesis of 3H-spiro [isobenzofuran-1,9'-xanthen]-3-one derivatives, phenols bearing electron-donating groups reacted successfully and afforded the products in high yields but phenols with electron-withdrawing groups increase the reaction rate in comparison to electron-donating groups.

The suggested mechanism could be explained by the treatment of differently substituted aldehydes depicted in Table 1 for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones derivatives (Scheme 4). Also, proposed mechanism for the synthesis of 3H-spiro[isobenzofuran-1,9'-xanthen]-3-one derivatives is depicted in (Scheme 5).

Comparing the efficacy and the applicability of this method with those of the previously reported methods for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]-

xanthen-11-ones and 3*H*-spiro[isobenzofuran-1,9'-xanthen]-3-one derivatives are depicted in Tables 3 and 4, respectively. As Tables 3 and 4 indicate, the cobalt hydrogensulphate catalyst is an efficient catalyst for the xanthen derivatives synthesis. Also our procedure is superior to the reported procedures in most of the terms such as the reaction conditions, the reaction temperatures, times and yields.

One of the advantages of cobalt hydrogensulfate is its ability to be recycled from the reaction medium. 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. After extraction of the reaction mixture, cobalt hydrogen sulfate was filtered, washed with ethyl acetate, and oven-dried to be used again.

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