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Antimony(III) sulfate catalysed one pot synthesis of 1,8-dioxo-octahydroxanthenes

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ABSTRACT

Antimony(III) sulfate was first used as a solid acidic catalyst for the synthesis of xanthenedione derivatives through the condensation reaction between aromatic aldehydes and dimedone. This method provides several advantages such as high yields, simple operation and short reaction time. As antimony(III) sulfate is an inexpensive recyclable catalyst, this synthesis is an eco-friendly reaction. © 2011 Trade Science Inc. - INDIA

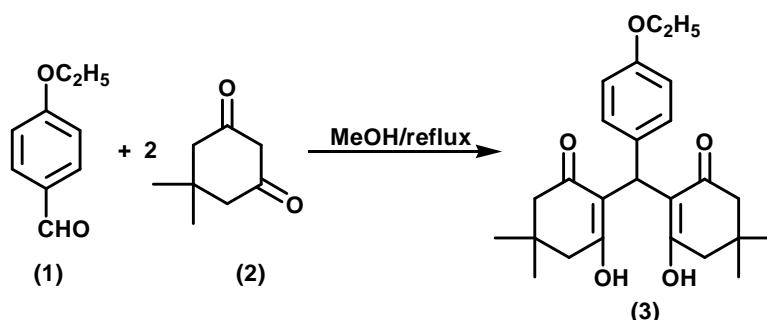
KEYWORDS

Antimony(III) sulfate;
Dimedone;
Xanthenedione derivatives;
Lewis acids;
Aromatic aldehydes;
One pot.

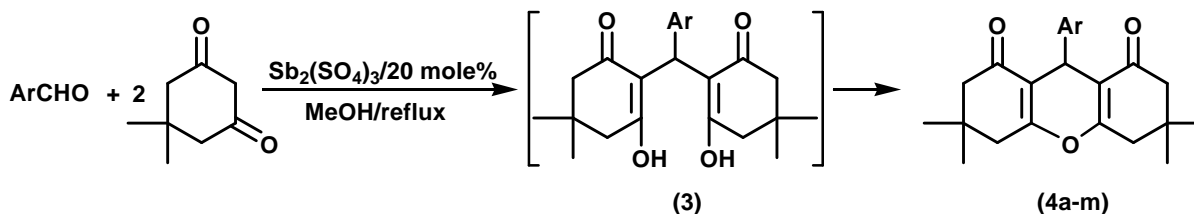
INTRODUCTION

Xanthene scaffold is present in a large number of naturally occurring, as well as synthetic compounds, and occupy a prominent position in medicinal chemistry^[1]. In particularly, xanthenediones constitute a structural unit in a number of natural products^[2] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring^[3]. The synthesis of xanthenediones usually involves the condensation of an appropriate active methylene carbonyl compound with an aldehyde, in the presence of a protonic or a Lewis acid. Among the lewis acids, InCl₃.H₂O^[4] and FeCl₃.6H₂O^[5] have been reported to catalyse this reaction efficiently. Although many other catalysts such as InCl₃.4H₂O in ionic liquid^[6], trimethylsilyl chloride^[7], *p*-docecyclbenzenesulfonic acid^[8,9], triethylbenzyl ammonium chloride^[10], and NH₂SO₃H/SDS^[11] have also been employed for the preparation of xanthenedione

derivatives, these catalysts have some or the other disadvantages like expensive, hazard, involve hazardous organic solvents, moisture sensitive and involve tedious workup. To overcome these problems eco-friendly catalysts like polyaniline-*p*-toluenesulfonate^[12], antimony trichloride/SiO₂^[13], and Fe³⁺/montmorillonite^[14] have appeared in literature. However in these reactions, the solid phase acid catalysts have to be prepared separately which will add an addition step in the synthesis of these xanthenes^[15]. Recently, we have described the application of antimony(III) sulfate as catalyst in imino Diels-Alder reaction^[16] and in the synthesis of bisindolyl methane^[17] and 2,3-disubstituted indole^[18]. In the synthesis of bisindolyl methane^[17], we have observed that antimony(III) sulfate significantly facilitates the condensation reaction between aldehydes and two molecules of indoles to offer bisindolyl methane in excellent yield over the other reported catalysts. Expecting the similar reaction between dimedone and aldehydes and in con-



Scheme 1 : Synthesis of xanthenedione intermediate derivatives



Scheme 2 : Synthesis of xanthenedione derivatives catalyzed by Antimony sulphate

tinuation of our work on antimony(III) sulfate as a solid acid catalyst in organic synthesis^[16-18], we have explored the possibility of using antimony(III) sulfate as solid acid catalyst in the synthesis of xanthenediones. Herein, we wish to report our preliminary results.

RESULTS AND DISCUSSIONS

The condensation between 4-ethoxybenzaldehyde and dimesone in methanol was chosen as the model reaction and antimony(III) sulfate has been used as a solid lewis acid catalyst to promote this reaction. Initial experiments were directed towards the optimization of the concentration of the catalyst and the results are tabulated in TABLE 1. The yields were in the range of 90-95% in all the experiments and as expected the reaction rate was varying. At 5 mol% concentration, the reaction took 4.30 h for completion and at 1 equivalent of catalyst; the reaction was completed in 30 min. To minimize the negative impact of the catalyst on the environment, we have carried out solvent optimization experiments using 20 mol % antimony(III) sulfate (TABLE 1).

Though the yields are good in all the solvents tried, the protic polar solvents like methanol and ethanol gave the best results (TABLE 2).

In our studies, one of the main aim of using antimony(III) sulfate as solid acid catalyst is because of

possibility of its reuse. Since antimony(III) sulfate is insoluble in many organic solvents, the catalyst could be easily recovered by filtration and reused. In the reaction between 4-ethoxybenzaldehyde and dimesone, the antimony(III) sulfate catalyst could be reused three times without appreciable losses of catalytic activity (TABLE 2, entry 7) (Scheme 1).

The mechanism of this reaction has been described^[8] in which, first intermediate (3) (Scheme 1) was formed through Knoevenagel addition between dimesone and aldehydes, subsequently water elimination of intermediate 3 resulted in the formation of desired xanthenedione (4). In catalyst free conditions (TABLE 2, entry 8), the reaction proceeds to result in the formation of the intermediate (3), which was isolated and characterized by ¹H NMR and mass spectral studies. In the other experiments catalyzed by antimony(III) sulfate, the initially formed intermediate (3) was rapidly undergoes dehydration to form the xanthenedione (TLC observation). By isolating the intermediate (3) in the absence of catalyst it was noticed that in this reaction, antimony(III) sulfate plays a catalytic role in accelerating the water elimination from intermediate (3) (Scheme 2).

With the optimized reaction condition in hand, we explored the generality of this reaction by choosing diversely substituted benzaldehydes and to get xanthenediones (4b-m) (TABLE 3). The yields are good in all these reactions and the reactions are com-

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TABLE 1 : Effect of catalyst in the reaction of benzaldehyde with dimedone in methanol at reflux temperature

Entry	Amount of catalyst mol % Sb ₂ (SO ₄) ₃	Time (h)	Yield / % ^a
1	5	4.30	90
2	10	3.30	90
3	15	2.30	92
3	20	2.00	95
4	30	1.00	95
5	40	0.45	95
6	50	0.45	95
7	100	0.30	95

^aIsolated yields

TABLE 2 : Screening of the effect of solvent for the synthesis of xanthenediones at reflux temperature

Entry	Solvent	Time(h)	Yield / % ^a
1	CH ₂ Cl ₂	2.00	80
2	Toluene	4.00	78
3	CH ₃ CN	2.00	86
4	DMF	2.30	80
5	THF	6.00	70
6	EtOH	2.00	95
7	MeOH	2.00	(95, 90,85) ^b
8	MeOH	0.50	90 ^c

^aIsolated yields, 20 mol% catalyst was used. ^bThe catalyst was recovered and reused for each of the three runs. ^cWith out catalyst, the product is intermediate 3 (Scheme 2)

pleted within 2 h (TABLE 3).

EXPERIMENTAL

All the melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and was purified by column chromatography. ¹H NMR spectra were recorded on a Bruker-400 Hz spectrometer using TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

Typical experimental procedure

A mixture of 4-ethoxy benzaldehyde (1 mmol), dimedone (2 mmol) and antimony(III) sulfate catalyst (20 mole %) in methanol (5 ml) was taken. The reaction mixture was refluxed on water bath for appropriate time. After the reaction is completed, the solid cata-

lyst was filtered and washed with methanol. To the methanolic solution 50 ml of ^{water} was added and the precipitated product was filtered and dried. The pure product was obtained by recrystallization from ethyl acetate. Using this general procedure xanthenediones (**4a-m**) were prepared (TABLE 3). The structures of these xanthenediones were confirmed by comparing the mp and spectral data with the reported ones in the literature.

For intermediate

To a mixture of 4-ethoxy benzaldehyde (1 mmol) and dimedone (2 mmol), methanol (5 ml) was added. The reaction mixture was refluxed on water bath for about 30 min. After the completion of the reaction, the reaction mixture was quenched with 50 ml of water, and the precipitated product was filtered and dried. The pure product was obtained by crystallization from ethyl acetate.

Analytical data for selected compounds

Compound (3a)

White solid, M.P. 160°C, ¹H NMR (300 MHz, CDCl₃): δ (ppm): 6.8 (d, J = 1.6 Hz, 2H), 6.7 (t, J = 2, 1H), 6.6 (d, J = 2.0 Hz, 1H), 5.8 (s, 1H), 3.9 (m, J = 6.8 Hz, 2H), 2.3 (d, J = 3.6 Hz, 6H), 2.0 (m, J = 2.4, 2H), 1.3 (m, J = 2.0 Hz, 3H), 1.0 (d, J = 12 Hz, 12H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 197.4, 197.4, 160.5, 160.5, 156, 131.1, 131.1, 130.7, 114.7, 114.7, 108.6, 108.6, 55.7, 55.3, 55.3, 48.1, 48.1, 27.6, 27.6, 27.6, 27.6, 26, 16.4, 16.4, 14.3. MS: m / z = 413.4 (M+1).

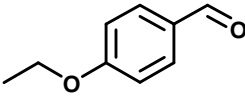
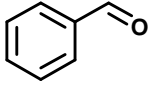
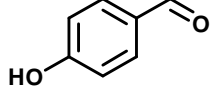
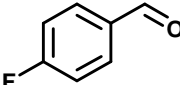
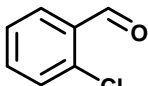
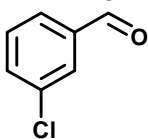
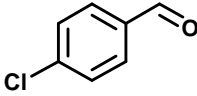
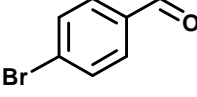
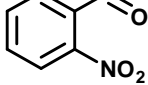
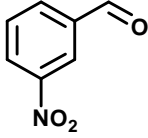
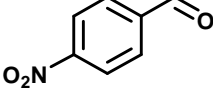
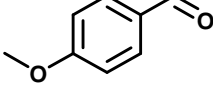
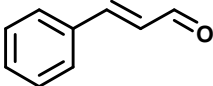
Compound (4a)

White solid, ¹H NMR (300 MHz, CDCl₃): δ (ppm): 0.9 (s, 6H, 2CH₃), 1.0 (s, 6H, 2CH₃), 1.3 (t, J = 6.9 Hz, 3H), 2.2 (d, J = 6.8, 4H), 2.26 (s, 4H), 3.98 (m, J = 6.9 Hz, 2H), 4.6 (s, 1H), 6.7 (d, J = 8.5 Hz, 2H), 7.2 (d, J = 8.58 Hz, 2H); ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 198.1, 198.1, 161.2, 161.2, 156.8, 131.8, 131.8, 131.3, 115.6, 115.6, 109, 109, 66, 55.8, 55.8, 48.5, 48.5, 28, 28, 28, 28, 26.5, 17, 17, 15. MS: m / z = 395.5 (M+1).

Compound (4b)

White solid. IR (KBr): 2954, 1664, 1364, 1199 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.8 (s, 6H, 2 x CH₃),

TABLE 3 : Synthesis of various xanthenedione derivatives catalyzed by Antimony sulphate

Entry	Aldehydes	Time (h)	Yield (%) ^b	mp(°C)		Ref.
				Found	Reported	
4a		2.00	95	211-212	-	-
4b		2.00	93	201-203	201-203	[7]
4c		2.00	95	246-249	245-250	[15]
4d		1.50	95	225-226	224-226	[4]
4e		2.50	91	224-227	225-227	[4]
4f		1.50	95	183-185	185-187	[15]
4g		1.50	95	229-231	230-232	[15]
4h		1.50	95	238-239	240-242	[7]
4i		2.50	75	257-258	258-262	[15]
4j		1.50	80	166-168	168-170	[19]
4k		1.50	80	221-224	222-224	[4]
4l		2.00	95	240-243	241-243	[4]
4m		2.00	94	175-176	175-177	[9]

^bIsolated yields

1.0 (s, 6H, 2 x CH₃), 2.0 (d, J = 16 Hz, 2H), 2.2 (d, J = 16 Hz, 2H), 2.4 (d, J = 7.8 Hz, 2H), 2.5 (d, J = 4.6 Hz, 2H), 4.5 (s, 1H), 7.1 (t, J = 6.7 Hz 1H), 7.2 (m, J = 7.5 Hz, 4H): ¹³C NMR (300 MHz, CDCl₃) δ (ppm):

198.1, 198.1, 161.2, 161.2, 126.8, 131.8, 131.8, 137.7, 129, 129, 109, 109, 66, 55.8, 55.8, 48.5, 48.5, 28, 28, 28, 28, 17, 17: MS: m / z = 351 (M+).

Compound (4m)

Yellow crystal: IR (KBr) : 3035, 2980, 1710, 1676, 1605, 1580, 1500, 1454, 1375, 1264, 1040, 970, 700 cm⁻¹: ¹H NMR (300 MHz, CDCl₃): δ = 1.0 (d, J = 4.0 Hz, 12H 4 x CH₃), δ = 2.0 (d, J = 16 Hz, 4H), δ = 2.2 (d, J = 8.2 Hz, 4H), δ = 4.1 (d, J = 4.7 Hz, 1H), δ = 6.2 (d, J = 6.6 Hz, 2H): ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 198.1, 198.1, 161.2, 161.2, 126.8, 128.8, 128.8, 134.7, 129, 129, 122.2, 129.9, 109, 109, 66, 55.8, 55.8, 48.5, 48.5, 28, 28, 28, 28, 17, 17: MS: m / z = 376 (M+).

CONCLUSION

In summary, we have demonstrated that the synthesis of xanthenediones from aromatic aldehyde and dimedone can be successfully conducted in the antimony(III) sulfate catalytic system. This procedure permits recycling of the catalyst without significant loss of catalytic activity. The experimental procedure is quite simple and convenient, and the reaction conditions are amenable to scale-up. Use of 20 mol % of catalyst and its reuse make this reaction environment friendly.

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