

Hydroxylamine-*O*-sulfonic Acid (HOSA): As a Task Specific Catalyst for the Synthesis of 1,8-Dioxo-octahydroxanthenes under Mild, Green and Solvent-free Condition

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A highly efficient procedure for the synthesis of 1,8-dioxo-octahydroxanthenes under mild, green and solvent-free condition by using HOSA as a dual role catalyst is described. This is the first report of catalytic activity of HOSA.

Keywords: Hydroxylamine-*O*-sulfonic acid, Solvent-free, Multi-component reaction, 1,8-Dioxo-octahydroxanthenes

INTRODUCTION

In recent years, multi-component reactions have awakened considerable interest in synthetic manners because of some advantages such as one-pot and simple route, high atomic economy, large scope of structural variables and accessible of complex target molecules [1].

Hydroxylamine-*O*-sulfonic acid is a dual role reagent that can be used both as nucleophile and electrophile in organic functional group transformations and heterocyclic chemistry according to the substrates used and reaction conditions. In this compound nitrogen atom can behave as either a nucleophilic center or an electrophilic center. Therefore, it can be expected that HOSA is being able to participate in a wide range of chemical reactions to afford synthetically interesting compounds [2]. Examples of all these reactions will be presented as follows: amination at carbon, nitrogen and sulfur [3-5], reduction [6] and organic functional group conversion, such as conversion of oximes to diazo compounds [7], methyl sulfones to sulfonamides [8] alkenes and carboxylic acids into primary amines [9,10] carbonyl compounds to oxime sulfonates [11] ketones to

oximes and amides [12]. HOSA has been used as alternative reagent for hazardous azides in classical Hofmann, Lossen and Curtis procedures [13]. Also, it has been reacted with β -(*N,N*-dimethylcarbamoyl-chalcogeno)-alkenyl ketone to yield the first twelve-membered ring periodic repetition of the *O*-Te-*N*-sequence [14]. Very recently, we have introduced the scope and limitation of HOSA *via* a mini review [15].

1,8-Dioxo-octahydroxanthenes are a privileged scaffold of heterocyclic compounds due to their numerous therapeutic and pharmaceutical activities. These versatile molecules have been used as antiviral and antibacterial agent [16,17]. In addition, they have been used as precursors for a wide variety of organic compounds [18] and dyes [19]. They have also potential to be used in laser technologies [20] and fluorescent materials [21]. Because of wide range of biological and industrial application of xanthenes, synthetic chemists have developed numerous protocols and have utilized various types of catalysts for the synthesis of these compounds [22-42]. On the other hand, considering of green chemistry disciplines and task-specific catalysts are an ethic sense of duty because catalysis has played a major role in the preventing of pollution in our environment. With this aim and our previously studies on

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design, synthesis, applications and development of solid acids, inorganic acid salts [43] and ionic liquids [44] herein, we wish to report synthesis of 1,8-dioxo-octa-hydroxanthenes by using HOSA as a task-specific catalyst under mild, green and solvent-free condition.

EXPERIMENTAL PROCEDURES AND MATERIALS

General: All chemicals were purchased from Merck and Fluka Chemical Companies. The known products were identified by comparison of their physical constant and spectral data with those reported authentic samples. Reaction progress and purity determination of the compounds were checked by TLC using silica gel SILG/UV 254 plates. The ^1H NMR (300.13) and ^{13}C NMR (75.47 MHz) were recorded on a Bruker spectrometer (δ in ppm). Melting points were recorded on a Buchi B-545 apparatus in open capillary tubes.

General Procedure for the Synthesis of 1,8-Dioxo-octahydroxanthenes

A round-bottomed flask containing a mixture of 1.2 moles of aromatic aldehydes, 2 moles of dimedone (0.28 g) and 5 mol% (6 mg) of HOSA as a dual role catalyst (Scheme 1), was subjected in an oil bath at 90 °C. The resulting mixture was stirred vigorously and the progress of the reaction was checked by TLC using a mixture of *n*-hexan: ethyl acetate as the solvent system. After completion of the reaction, for removing of catalyst from reaction mixture, 5 ml of distilled water was added to the reaction mixture. Then, the crude product was collected by filtration, air dried and recrystallized from EtOH to afford pure

product with high yields.

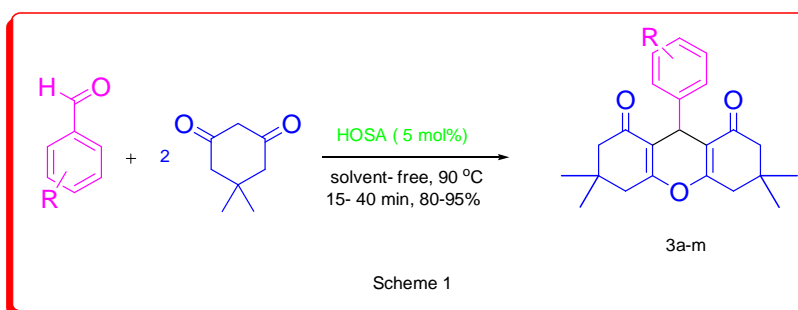
Selected Characterization Data

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (3a). White powder, M. P.: 205-207 °C. FT-IR (KBr): ν (cm^{-1}) = 2958, 1662, 1625, 1454, 1361, 1199, 699. ^1H NMR (DMSO- d_6 , 300.13 MHz): δ (ppm) = 0.89 (s, 6H, CH_3), 1.03 (s, 6H, CH_3), 2.07 (d, 2H, CH_2 , J = 16.2 Hz), 2.26 (d, 2H, CH_2 , J = 16.2 Hz), 2.53-2.60 (m, 4H, CH_2), 4.52 (s, 1H, CH), 7.06-7.10 (m, 1H, C_6H_5), 7.15-7.23 (m, 4H, C_6H_5). ^{13}C NMR (DMSO- d_6 , 75.47 MHz): δ (ppm) = 26.4, 28.7, 31.2, 31.8, 39.7, 50.0, 114.4, 126.2, 127.8, 128.0, 144.2, 162.9, 196.0.

3,3,6,6-Tetramethyl-9-(2-bromophenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (3i). White powder, M. P.: 225-227 °C. FT-IR (KBr): ν (cm^{-1}) = 2962, 1667, 1627, 1467, 1356, 1203, 746. ^1H NMR (DMSO- d_6 , 300.13 MHz): δ (ppm) = 0.90 (s, 6H, CH_3), 1.02 (s, 6H, CH_3), 2.02 (d, 2H, CH_2 , J = 16.1 Hz), 2.24 (d, 2H, CH_2 , J = 16.1 Hz), 2.43-2.60 (m, 4H, CH_2), 4.81 (s, 1H, CH), 7.01 (t, 1H, J = 7.3 Hz, C_6H_4), 7.20-7.26 (m, 2H, C_6H_4), 7.43 (d, 1H, J = 7.9 Hz, C_6H_4). ^{13}C NMR (DMSO- d_6 , 75.47 MHz): δ (ppm) = 26.5, 28.7, 31.7, 32.5, 50.1, 113.5, 123.5, 127.1, 128.0, 132.8, 142.6, 163.1, 195.8.

RESULTS AND DISCUSSION

Development of task-specific catalysts and their structural diversity could be achieved *via* a combination of the different structural moiety or functional group within a catalyst core. As you have seen, HOSA has both amine and sulfonic acid moieties within its structure. By considering the above-mentioned synthetic strategy, in the course of a



decade of our investigation on designing, synthesis and applications of solid acids and inorganic acid salts [43], we decide to use HOSA as a task-specific catalyst with dual ability for the preparation of 1,8-dioxo-octahydroxanthenes under mild, green and solvent-free condition. First of all, to find the optimized conditions of the reaction for the

synthesis of target molecules, the reaction of benzaldehyde **1** and dimedone **2** was selected as a model reaction (Scheme 2).

As shown in Table 1, the model reaction was carried out in different temperatures and loads of catalyst. The best result from the model reaction was obtained with

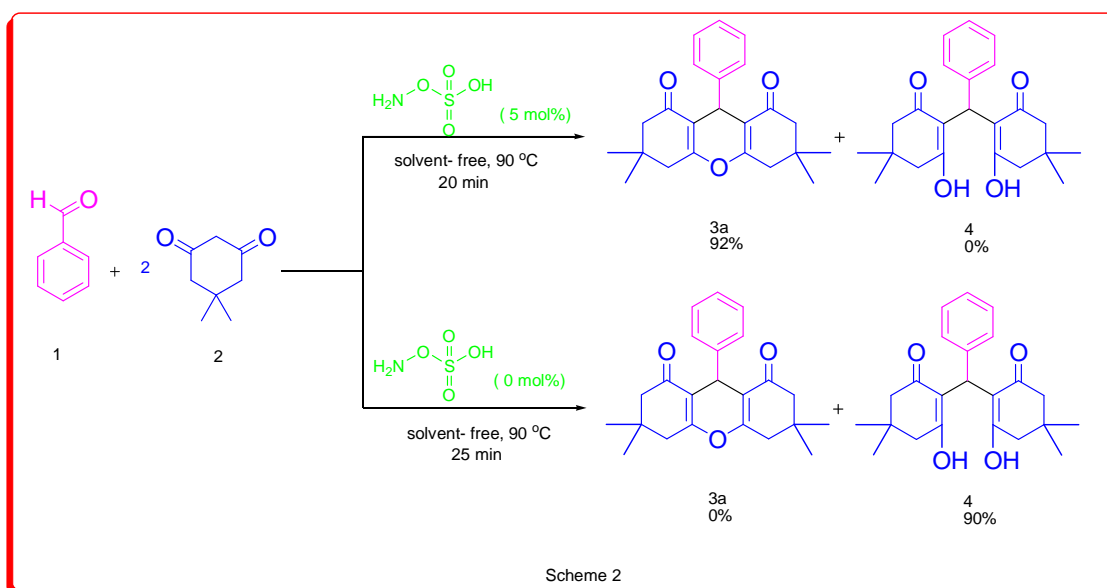


Table 1. Optimization of the Reaction Conditions for the Synthesis of 1,8-Dioxooctahydroxanthenes

Entry	Amount of catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%) ^a	
				3a	4
1	10	r.t.	120	Trace	-
2	10	50	90	40	-
3	10	70	35	85	-
4	10	90	20	90	-
5	10	110	15	90	-
6	7	90	25	91	-
7	5	90	20	92	-
8	3	90	30	88	-
9	-	90	25	-	90

^aRefers to isolated yields.

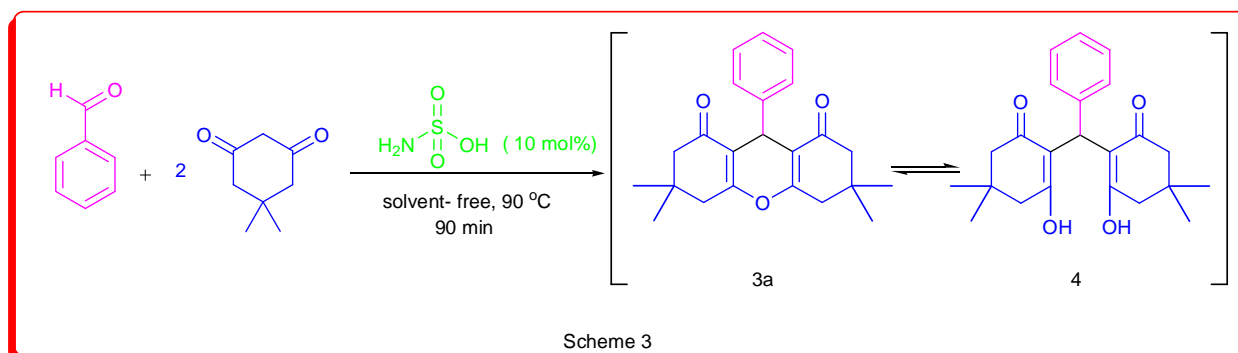
catalytically amount of HOSA in 90 °C (Table 1, Entry 7). Also, in attempting to find the optimized condition, we have tested the model reaction in the absence of HOSA at 90 °C, surprisingly, when the reaction was carried out without using catalyst, there was no sign of compound **3a** and the compound **4** was produced as the main product with a good yield in a relatively short reaction time. This observation is

in close agreement with results reported in the literature [45] (Scheme 1 and Table 1, Entry 9). Afterward, in order to assess the applicability and scope of the catalyst, a wide range of arylaldehydes with electron withdrawing and releasing group were reacted with dimedone in optimized reaction condition. The obtained results are depicted in Table 2.

Table 2. Synthesis of 1,8-Dioxo-octahydro-xanthenes

Entry	R	Product	Time (min)	Yield (%) ^a	M. P. (°C) found [Lit] ^{Ref.}
1	H	3a	35	92	205-207 [199-201] ²³
2	4-Me	3b	20	90	206-208 [216-218] ²³
3	2,4-Cl ₂	3c	30	87	248-250 [253-254] ⁴⁶
4	4-NO ₂	3d	20	92	228-230 [224-226] ²³
5	4-OMe	3e	35	80	250-251 [243-245] ²³
6	4-Cl	3f	25	92	236-238 [229-231] ²³
7	3-NO ₂	3g	25	95	154-156 [164-166] ²³
8	4-F	3h	15	95	223-225 [226-227] ⁴⁶
9	2-Br	3i	30	89	225-227 [226-229] ⁴⁶
10	3,4-(OMe) ₂	3j	35	88	178-180 [178-180] ²³
11	4-Br	3k	15	90	242-244 [242-244] ²³
12	4-OH	3l	30	85	240-242 [247-248] ⁴⁶
13	4-CN	3m	20	90	223-225 [220-222] ²³

^aRefers to isolated yields.



In another attempt for the synthesis of 1,8-dioxo-octa-hydroxanthenes, due to structural similarity of the HOSA and sulfamic acid (SA), we have tested the reaction between benzaldehyde and dimedone for the synthesis of compound **3a** using SA as catalyst (5 mol% (0.005 g)), 10 mol% (0.01 g) and 15 mol% (0.0146 g) in an oil bath at 90 °C. In all cases a mixture of compounds **3a** and **4** were obtained. Typically, for the use of 10 mol% of SA, in the beginning of the reaction, compound **4** was produced as the main product. But, when the reaction continued for 90 min in the same condition, compound **3a** has emerged as the main product with yield 82%. It is believed that there is equilibrium between two products, so that, in the beginning of the reaction, the equilibrium favored the formation of the compound **4**, but as the reaction continued, the catalyst through dehydration, move the equilibrium toward the formation of compound **3a** as the main product.

Also, in order to evaluate the efficiency of the current

procedure for the synthesis of 1,8-dioxo-octa-hydroxanthenes, we have compared our obtained results with those of the other protocols reported in the literature (Table 3). The collected data have shown that the current procedure is comparable with other reported procedures.

Plausible Mechanism for the Synthesis of Target Molecules in the Presence of HOSA

The above mentioned obtained results for SA and HOSA guide us to different mechanistic pathways for them. The authors believed that the α -effect associated with the HOSA structure make its nitrogen atom more nucleophile than the nitrogen atom in SA and this property allows HOSA acts as a dual role catalyst in plausible mechanism. But in the case of SA, only the Brønsted acidity plays the key role in catalysis of the reaction. A proposed mechanism for the synthesis of target molecules **3a-m** in the presence of HOSA is depicted in Scheme 4. The synthesis of 1,8-

Table 3. Comparison of HOSA and other Systems for the Synthesis of Compound **3a**

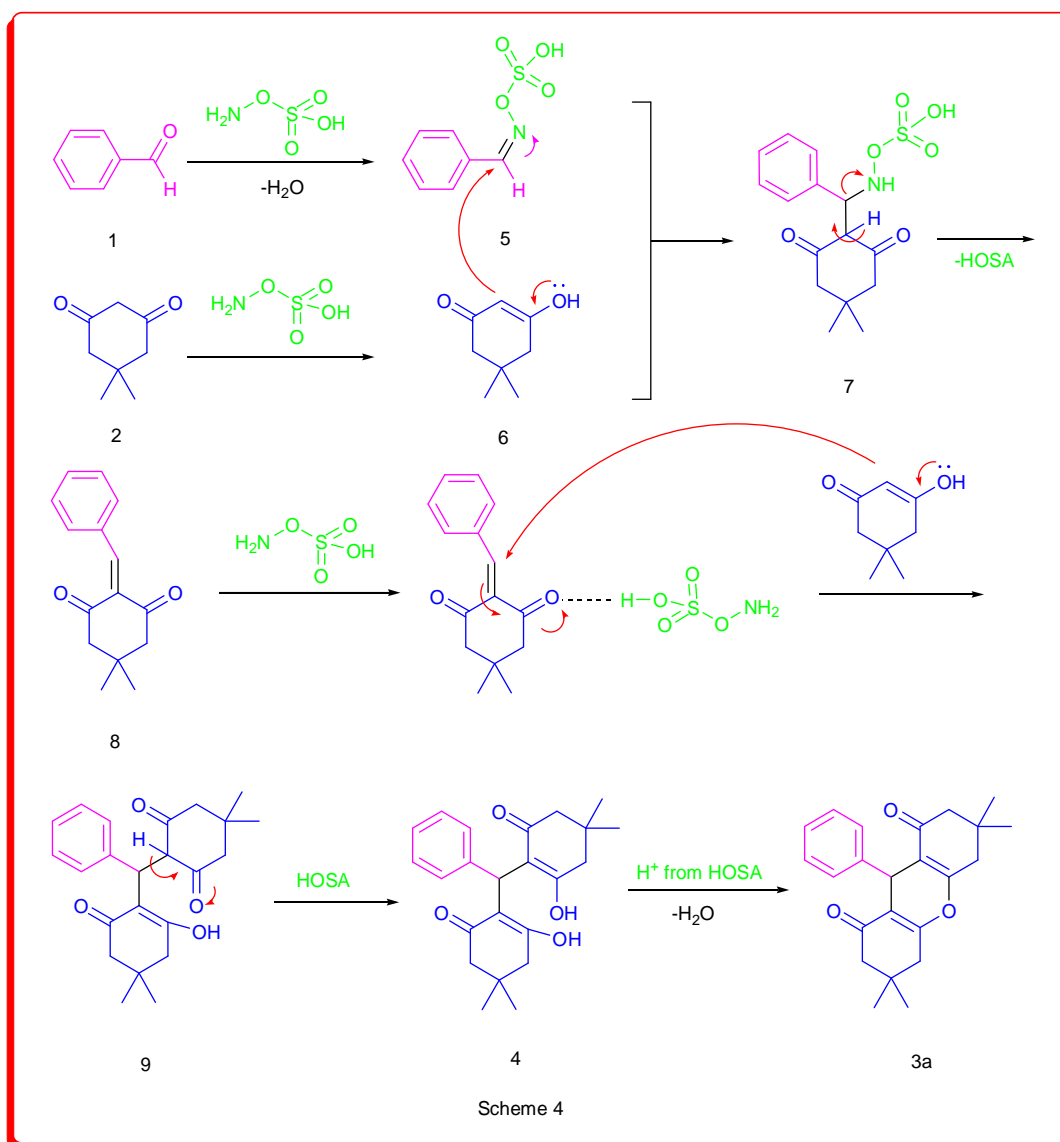
Entry	Reaction condition	Time (min)	Yield (%)	Lit.
1	[H-NMP] ⁺ [HSO ₄] ⁻ (20 mol%), H ₂ O	50	86	47
2	InCl ₃ or P ₂ O ₅ , solvent-free, 100 °C	36 or 40	83 or 80	48
3	Ceric(IV) ammonium nitrate, 2-propanol, 50 °C	35	98	49
4	NSPVPC (20 mg), Solvent-free, 100 °C	10	98	50
5	[Et ₃ N-SO ₃ H]Cl (25 mol%), Solvent-free, 80 °C	60	97	23
6	[CMIM][HSO ₄] (10 mol%), 70 °C, Water	150	85	51
7	Nano Fe ₃ O ₄ @SiO ₂ -SO ₃ H, Solvent-free, 110 °C	4	97	52
8	[DDPA][HSO ₄], Water, 100 °C	60	93	53
9	Molybdate sulfonic acid (5 mol%, Solvent-free, 100 °C)	60	96	54
10	SBNPSA (0.03 g), EtOH, Reflux	120	93	55
11	SiCl ₄ , ClCH ₂ CH ₂ Cl	180	90	56
12	[Et ₃ NH][H ₂ PO ₄] (0.4 g), Solvent-free, 100 °C	5	96	57
13	CAN/HY-zeolite, Solvent-free, 80 °C	90	88	58
This work	HOSA (5 mol%), Solvent-free, 90 °C	20	92	-

dioxooctahydroxanthene derivative **3a** is believed to proceed *via* several steps as follows: Initially, similar to reported literatures [59,11], activation of benzaldehyde **1** has occurred *via* reaction of its carbonyl group and HOSA to generate the related oxime-*O*-sulfonic acid **5**. Then, the first molecule of enol form of dimedone **6** reacts with intermediate **5** to afford Knoevenagel product **7** followed by a conjugate Michael addition of second molecule of enol form of dimedone **6** with intermediate **8** to generate intermediate **9**, which upon dehydration affords cyclic

compound **3a** as a target molecule.

CONCLUSIONS

In conclusion, we have developed a new procedure for the preparation 1,8-dioxooctahydroxanthenes (**3a-m**) using Hydroxylamine-*O*-sulfonic acid as an efficient and powerful catalyst. The condensation of dimedone with a good range of arylaldehydes in the presence of a catalytic amount of HOSA under mild, green and solvent-free condition were



occurred. To the best of our knowledge, this is the first report of catalytic activity of HOSA. The significant advantages of this study are environmentally benign, biological-based catalysts, low cost, cleaner reaction profile, high yield, short reaction time, simple work-up and close agreement with the green chemistry disciplines.

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