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Clean synthesis of 1,8-dioxo-octahydroxanthene derivatives using NBS as an efficient and almost neutral catalyst in aqueous media

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Abstract

An efficient one-pot condensation for the synthesis of 1,8-dioxo-octahydroxanthene is achieved through a condensation of aryl aldehydes and 5,5-dimethyl-1,3-cyclohexandione in the presence of NBS. This method enjoys several advantages such as low cost, simple work up procedure and safe reaction condition. In addition, water was chosen as a green solvent.

Keywords: One-pot, NBS, 1,8-dioxo-octahydroxanthene, Organocatalyst, Aqueous media

1. Introduction

The synthesis of xanthenes derivatives has been of considerable interest to chemists because of their wide range of biological and pharmaceutical properties such as antiviral [1], antibacterial [2], and anti-inflammatory activities [3]. Furthermore, these compounds have been used as dyes [4], in laser technology [5], pH-sensitive fluorescent materials for the visualization of biomolecular assemblies [6]. xanthenediones a closely related group of organic compounds constitute a structural unit in a number of natural products [7] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring [8].

Up to now, several methods are developed for the preparation of 1,8-dioxo-octahydroxanthene (xanthenediones). The conventional procedures involve acid- or base-catalyzed condensation of appropriate active methylene carbonyl compounds with aldehydes [9]. However, these methods are plagued by the limitation of prolonged reaction times, poor yields and side reactions of aldehydes. More recent synthetic methods are reported using *p*-dodecylbenzenesulfonic acid (DBSA) in aqueous media [10], namely *p*-toluenesulfonic acid (*p*–TsOH) in organic solvent [11], heterogeneous catalysts ($NaHSO_4$-SiO_2 and silica chloride) [12], $InCl_3 \cdot 4H_2O$ in ionic liquid [13], Amberlyst-15 [14], polyaniline-*p*-toluenesulfonate salt [15] and PPA-SiO_2 [16]. These methods also suffer from some disadvantages such as the use of toxic solvents, use of special apparatus, and toxic catalysts. Thus, the development of a new catalyst for the synthesis of xanthenediones derivatives is highly desirable.

Most chemical reactions of organic substances conducted in the laboratory as well as in industry need organic solvents as reaction media, although water is safe, benign, environmental friendly, and cheap compared with organic solvents. Since 1980, Breslow had discovered that Diels–Alder reaction performed in water can be subject to huge accelerations [17]. The

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observation led to increased interest from synthetic organic chemists in organic reactions in water.

Soon it was discovered that other organic reactions, like the Claisen rearrangement [18], the aldol condensation [19], and the benzoin condensation [20] exhibit rate enhancements in water. To date, many more organic transformations have been carried out in water [21]. Also the use of organic molecules as catalysts has become an attractive alternative to the traditional metal-catalysts. Interest in the field of organocatalysis has increased spectacularly in the last few years as the result of both the novelty of the concept and more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions [22]. N-Bromosuccinimide (NBS) is one such catalyst, that which it has been known as a brominating agent for long time it has recently received considerable attention as a catalyst in various organic transformations [23]. Furthermore, it is also used in oxidation and free radical reactions under mild and convenient conditions to afford the desired products in excellent yields and with high selectivities. However, there are no examples of the use of NBS as a catalyst for the synthesis of xanthenediones.

2. Experimental

The products were isolated and characterized by physical and spectral data. ^{1}H NMR spectra were recorded on Bruker Avance-300 MHz spectrometers using 7–10mM solutions in $CDCl_3$ in the presence of tetramethylsilane as an internal standard. IR spectra were recorded using a Perkin-Elmer 843 spectrometer with KBr plates. Melting points were determined on an Electro thermal 9100, and are not corrected.

2.1. General procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives 3

Method A: A mixture of a substituted benzaldehyde (1 mmol), dimedone (2 mmol), NBS (0.2 mmol) and ethanol (10mL) was stirred at reflux condition for an appropriate time (Table 2). After completion of the reaction, the mixture was kept at room temperature and the resulting crystalline product was collected by filtration. The product was found to be pure and no further purification was necessary.

Method B: A mixture of substituted benzaldehyde (1 mmol), dimedone (2 mmol) and NBS (0.2 mmol) in DMAC (2mL), contained in a tall beaker, was placed in the microwave oven. The beaker was covered with a watch glass and irradiated at 600 W powers for an appropriate time (Table 2). To control the evolution of DMAC from the reaction mixture and to prevent splashing, irradiation sequences reaction was interrupted after every 20 s. Then the reaction mixture was allowed to cool to r.t., and H_2O (5 mL) was added. The precipitate was filtered off and washed with H_2O. After recrystalization from ethanol.

Method C: A mixture of a substituted benzaldehyde (1 mmol), dimedone (2 mmol), NBS (0.2 mmol) and water (10 mL) was stirred at reflux condition for an appropriate time (Table 2). After completion of the reaction, the mixture was kept at room temperature and the resulting solid product was collected by filtration. The product was found to be pure and recrystalization from ethanol.

Compound 3i (Table 2): with solid; IR (KBr): ν_{max}/cm^{-1} 3005, 2959, 2873, 1674, 1660, 1625, 1605, 1584, 1486, 1447, 1360, 1274, 1201, 1164, 1139, 1047, 1001, 9001, 862, 801, 768, 691, 654, 574; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.00 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.21 (ABq, 4H, J = 16.4 Hz, $2CH_2$, H-4, H-5), 2.45 (s, 4H, $2CH_2$, H-2, H-7), 3.77 (s, 3H, OCH_3), 4.74 (s, 1H, H-9), 6.63-6.67 (m, 1H, ArH), 6.86-6.89 (m, 2H, ArH), 7.10-7.15 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.41, 29.22, 31.76, 32.18, 40.85, 50.74, 55.09, 55.13, 111.80, 114.29, 115.54, 120.87, 128.87, 145.68, 159.31, 162.25, 196.39; Anal. Calcd for $C_{24}H_{28}O_4$: C, 69.33; H, 9.33; Found: C, 68.99; H, 9.41.

Compound 3j (Table 2): with solid; IR (KBr): ν_{max}/cm^{-1} 3019, 2967, 2890, 1679, 1667, 1628, 1613, 1589, 1508, 1468, 1429, 1364, 1301, 1272, 1217, 1201, 1170, 1140, 1048, 1005, 933, 836, 578; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.95 (s, 6H, $2CH_3$), 1.09 (s, 6H, $2CH_3$), 2.18 (ABq, 4H, J = 16.4 Hz, $2CH_2$, H-4, H-5), 2.40 (ABq, 4H, J = 17.4 Hz, $2CH_2$, H-2, H-7), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.77 (s, 1H, H-9), 6.32 (d, 1H, J = 2.3 Hz, ArH), 6.43 (m, 1H, ArH), 7.3 (d, 1H, J = 8.3 Hz ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.67, 29.05, 29.54, 32.12, 40.93, 50.78, 54.99, 55.12, 98.53, 103.91, 113.71, 123.14, 132.55, 158.42, 159.44, 162.78, 196.73; Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.17; H, 7.32; Found: C, 73.26; H, 7.45.

Compound 3q (Table 2): with solid; IR (KBr): ν_{max}/cm^{-1} 3042, 2972, 2888, 1748, 1721, 1654, 1604, 1475, 1424, 1396, 1328, 1304, 1244, 1207, 1156, 1053, 973, 850, 636, 566; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.90 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.17 (s, 6H, $2CH_3$) 2.21 (m, 4H, $2CH_2$), 2.69 (m, 3H), 3.26 (d, 1H, J =14.7 Hz), 4.81 (s, 1H, H-9), 7.77 (sbr, 2H, ArH), 8.70 (sbr, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.41, 28.41, 28.78, 30.02, 30.82, 34.44, 37.25, 49.88, 50.76, 52.15, 53.95, 102.65, 113.18, 125.57, 145.08, 151.84, 177.95, 192.88, 198.07, 198.11; Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99; Found: C, 75.83; H, 6.99; N, 4.08.

Compound 3r (Table 2): with solid; IR (KBr): ν_{max}/cm^{-1} 3069, 2971, 2940, 2885, 1679, 1667, 1630, 1605, 1511, 1466, 1364, 1199, 1167, 1142, 1005, 829, 747, 484; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 0.98 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.19 (ABq, 4H, J = 16.3 Hz, $2CH_2$, H-4, H-5), 2.51 (s, 4H, $2CH_2$, H-2, H-7), 4.92 (s, 1H, H-9), 7.36-7.40 (m, 2H, ArH), 7.44-7.47 (m, 1H, ArH), 7.69-7.75 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.32, 29.30, 31.98, 32.21, 40.89, 50.72, 115.59, 125.29, 125.58, 126.87, 127.13, 127.45, 127.68, 127.97, 132.34, 133.37, 141.62, 162.31, 196.40; Anal. Calcd for $C_{27}H_{28}O_3$: C, 81.00; H, 7.00; Found: C, 81.13; H, 7.07.

3. Results and discussion

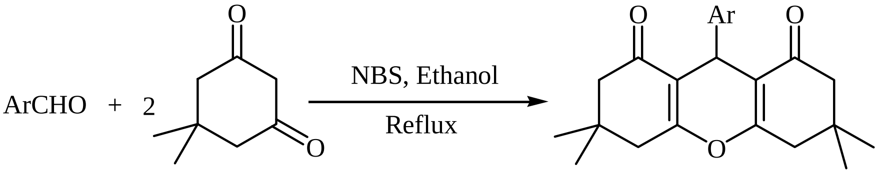
As part of our ongoing research concerning the use of economically and easily available materials as catalysts for various organic transformations [24], we wish to report a simple and efficient use of NBS as a catalyst in synthesis of 1,8-dioxo-octahydroxanthene derivatives, under mild conditions. In this paper physical and spectroscopic data including CHN analysis are reported for new compounds.

Initially, the reaction was performed by reacting dimedone (2equiv.) and benzaldehyde (1equiv.) in the presence of 2 mol % NBS in ethanol at room temperature. Under these conditions, only a trace amount of product was obtained after a 6h priod. The conditions for this transformation were optimized and the results are shown in Table 1.

Table 1
Optimization of reaction condition

Entry	Amounts of NBS	Condition	Yield (%)
1	0 mol %	Reflux/ethanol/20h	0
2	2 mol %	50°C/ethanol/6h	tr
3	2 mol %	Reflux/ethanol/6h	15
4	5 mol %	Reflux/ethanol/6h	30
5	10 mol %	Reflux/ethanol/6h	55
6	15 mol %	Reflux/ethanol/4h	80
7	20 mol %	Reflux/ethanol/4h	94
8	20 mol %	MW/DMAC/5min	90
9	20 mol %	Reflux/water/2h	92

No product was obtained in the absence of the catalyst (Table 1, entry 1) even when the reaction time was extended to 20h, thus demonstrating the necessity of NBS. The amount of catalyst required for the transformation was investigated by the use of 5–20 mol % of catalyst to aldehyde. Under these conditions, the yield of the product was in the range of 30–94% (Table 1, entries 4–7). The use of 20 mol % NBS resulted in the best yield (94%) for a 4 hour reaction at reflux condition (Table 1, entry 7). Thus, under the optimized reaction conditions, dimedone (2 mmol) and substituted benzaldehydes (1 mmol) were mixed with NBS (0.2 mmol) and stirred at reflux condition for 3-4 h. After completion of the reaction (monitored by TLC), the mixture was kept at room temperature and the resulting crystaline product was collected by filtration (Scheme 1).



1 **2** **3**

Scheme 1

As shown in Table 2, aromatic aldehydes having both electron donating or withdrawing groups reacted readily with dimedone to afford the corresponding 1,8-dioxo-octahydroxanthenes in 82-96% yields. A plausible explanation for NBS role is the generation of Br^+ ions which in turn activate the aldehyde for further reaction with dimedone.

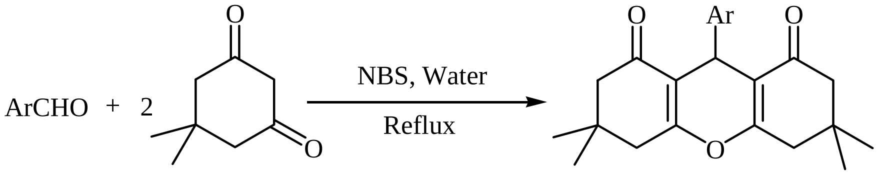
Table 2
Preparation of 1,8-dioxo-octahydroxanthenes catalyzed by NBS in ethanol and DMAC

Product	Ar	Time (min)		Yield (%) [a]		Mp (°C)	
		Method A	Method B	Method A	Method B	Found	Reported
3a	C_6H_5-	4	5	94	90	204-205	202-204 [10a]
3b	4-ClC_6H_4-	3	5	94	93	225-226	228-230 [10a]
3c	2-ClC_6H_4-	4	6	88	85	228-230	228-230 [10a]
3d	4-BrC_6H_4-	3	4	94	90	233-235	234-236 [13]
3e	4-FC_6H_4-	3	4	96	90	224-225	224-226 [13]
3f	4-MeC_6H_4-	4	5	92	85	218-220	217-218 [10a]
3g	4-$MeOC_6H_4$-	4	6	88	82	243-245	242-244 [10a]
3h	2-$MeOC_6H_4$-	4	8	85	80	184-185	190-191 [25]
3i	3-$MeOC_6H_4$-	4	8	82	80	177-180	---
3j	2,4-$MeOC_6H_3$-	4	8	85	80	209-211	---
3k	4-OHC_6H_4-	4	6	85	81	243-245	246-248 [10b]
3l	2-OHC_6H_4-	4	8	82	75	202-205	205-206 [25]
3m	4-$NO_2C_6H_4$-	3	5	94	90	226-227	226-228 [10a]
3n	3-$NO_2C_6H_4$	3	5	92	87	168-170	168-170 [10a]
3o	C_6H_5CH=CH-	4	6	90	85	177-178	175-177 [10a]
3p	4-$Me_2NC_6H_{4-}$	4	6	89	85	226-229	226-228 [10a]
3q	4-pyridyl-	4	6	90	86	218-220	---
3r	2-naphthyl-	4	6	90	84	194-196	---

[a] Isolated yield

Another explanation for this process is that NBS probably generates small quantities of HBr or Br_2, which may be the actual catalysts for the reaction.

Our results show high yields of products in the presence of ethanol as well as *N,N*-dimethylacetamide (DMAC). It is reported that Br^+ is generated in DMAC and therefore we conclude that either in both media the active agent is Br^+ ion or that Br^+ ion is active in DMAC and HBr is the active agent in a protic solvent such as ethanol [23b]. This fact that water is very excellent solvent for green chemistry causes we select it as green solvent for this reaction (Scheme 2).



1 2 3

Scheme 2

Table 3 shows results give this reaction in water. Our results show that water is the better solvent than ethanol because the reaction time is less and the yields approximately same in method A. We propose that the reaction proceeds via a Knoevenagel condensation followed by Michael addition and cyclization (Scheme 3).

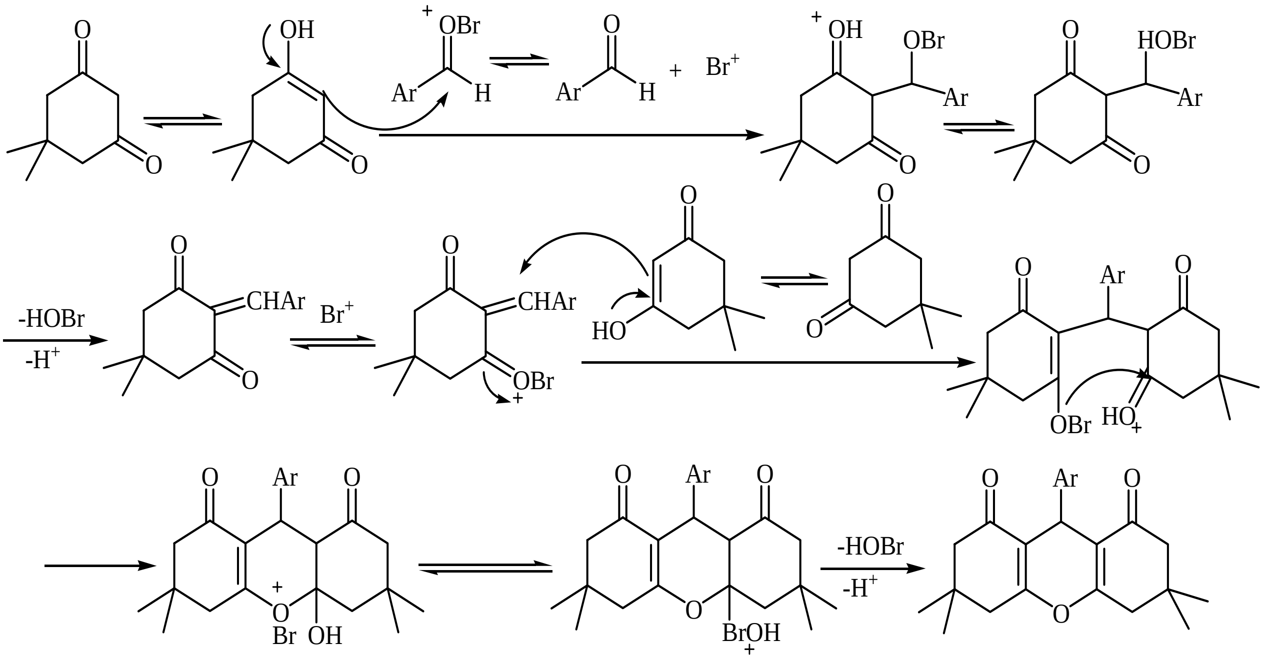
Table 3
Preparation of 1,8-dioxo-octahydroxanthenes catalyzed by NBS in water

Product	Ar	Time (h)	Yield (%) [a]
3a	C_6H_5-	2	92
3b	4-ClC_6H_4-	1.5	92
3c	2-ClC_6H_4-	2	90
3d	4-BrC_6H_4-	1.5	94
3e	4-FC_6H_4-	1.5	95
3f	4-MeC_6H_4-	2	92
3g	4-$MeOC_6H_4$-	2	88
3h	2-$MeOC_6H_4$-	2	86
3i	3-$MeOC_6H_4$-	2	82
3j	2,4-$MeOC_6H_3$-	2	84
3k	4-OHC_6H_4-	2	84
3l	2-OHC_6H_4-	2	80
3m	4-$NO_2C_6H_4$-	1.5	92
3n	3-$NO_2C_6H_4$	1.5	90
3o	C_6H_5CH=CH-	2	88
3p	4-$Me_2NC_6H_4$-	2	90
3q	4-pyridyl-	2	91
3r	2-naphthyl-	2	91

[a] Isolated yield

4. Conclusion

In conclusion, I have successfully developed a simple and efficient crossed aldol methodology followed by a Micheal addition for the synthesis of 1,8-dioxo-octahydroxanthene derivatives from dimedone under reflux conditions, using cheap and readily available NBS as a catalyst. This simple procedure can be applied to the synthesis of a wide variety of xanthenediones in good to excellent yields. Further applications of this catalytic system are currently underway. In addition, water was chosen as a cheap and green solvent.



Scheme 3

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