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RESEARCH ARTICLE

An Efficient Synthesis of 1, 8-Dioxooctahydroxanthenes Catalysed by Thiourea Dioxide (TUD) in Aqueous Media

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Abstract: A simple and highly efficient protocol for the synthesis of biologically active 1,8-dioxo-octahydroxanthenes from various aromatic aldehydes with dimedone by using thiourea dioxide (TUD) as catalyst in aqueous media is reported. This protocol gives wide range of xanthene derivatives with high yield.

Keywords: 1,8-Dioxooctahydroxanthenes, Dimedone, Aromatic aldehydes, Thiourea dioxide, TUD

Introduction

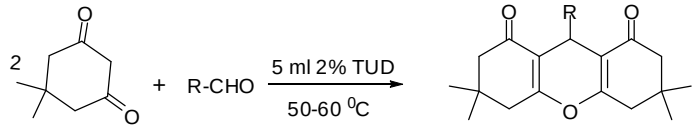
Xanthene and their derivatives are an important family of organic compounds because they have wide range of biological and pharmaceutical properties such as antibacterial[1], antiviral[2], anti-inflammatory[3], anti-depressants and antimalarial agents[4]. Also, they are as structural unit in a number of natural products[5] and santalin pigments isolated from a number of plant species are major sources for xanthenes[6]. Furthermore, these compounds are utilized in industries as leuco-dye[7], in laser technology[8], as pH sensitive fluorescent materials for the visualization of biomolecular assemblies[9] and used in photodynamic therapy[10]. Recently, xanthenes have been used as rigid carbon skeletons for the construction of new chiral bidentate phosphine ligands with potential applications in catalytic processes[11].

Even though, various methods have been reported for preparation of xanthenes and substituted xanthenes, the classical method for the synthesis of 1,8-dioxo-octahydro xanthenes involves the condensation of appropriate active methylene carbonyl compounds with aldehydes[12]. For this purpose, two molecules of dimedone (5,5-dimethyl-1,3- cyclohexane dione) reacts with various aromatic aldehydes[13], by using of different Lewis acid catalysts such as triethylbenzyl ammonium chloride[14], *p*-dodecyl benzenesulfonic acid[15], diammonium hydrogen phosphate under various conditions[16], sulfonic acid under ultrasonic irradiation[17], ionic liquids[18], Amberlyst-15[19], $NaHSO_4$-SiO_2 or silica chloride[20], phosphomolybdic acid

supported on silica gel[21], nanosized MCM-41-SO_3H under ultrasonic irradiation[22], sulfonic acid on silica gel[23], Dowex-50W ion exchange resin under solvent-free conditions[24], $HClO_4$–SiO_2, ZnO[25] and ZnO acetyl chloride[26] and heteropoly acid supported MCM-41[27]. Each of these methods have their own advantages but also suffer from one or more disadvantages such as prolonged reaction time, tedious work-up processes, low yield, lack of easy availability/preparation of starting materials and hazardous reaction conditions.

Thiourea dioxide (TUD)[28] easily prepared by the oxidation of thiourea with hydrogen peroxide is highly stable and possesses the ability to activate organic substrates through hydrogen bonding. Owing to the presence of two extra oxygen atoms it forms strong hydrogen bonding and can provide higher activation than the corresponding thiourea. In addition, thiourea dioxide is insoluble in common organic solvents and therefore can easily be recovered at the end of the reaction for its reuse. Despite its high potential, the use of thiourea dioxide as organocatalyst for organic reactions is not much reported in the literature[29].

In continuation of our interest on synthesis of heterocyclic compounds, we report here a new, green and highly efficient method for the synthesis of 1,8-dioxooctahydroxanthenes *via* the condensation of dimedone with aldehydes using TUD as catalyst in aqueous media at 50-60 °C (Scheme 1).



Scheme 1. Synthesis of 1,8-dioxo-octahydroxanthenes using TUD as catalyst

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies and they were used as received. All compounds are known and their structures were identified by comparing their melting points and ^1H and ^{13}C NMR data with those reported in the literature. The ^1H NMR (500 MHz, 400 MHz) and ^{13}C NMR (125 MHz, 100 MHz) spectra were recorded on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Tetramethylsailane (TMS) was used as internal standard. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General procedure for the preparation of 1,8-dioxo-octahydroxanthenes using Thiourea dioxide as catalyst

A mixture of dimedone (2 mmol), aromatic aldehyde (1 mmol) and 5 mL of 2% thiourea dioxide(TUD) aqueous solution in a round-bottomed flask connected to a reflux condenser, was heated and stirred in an oil-bath (50-60 °C) for appropriate time shown in Table 2. After completion the reaction as monitored by TLC, cool the reaction mass and filter the obtained solid and recrystallized in ethanol to afford the pure products.

Representative spectral data of the products

3,3,6,6-Tetramethyl-9(phenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 1)

^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (s, 6H), 1.04 (s, 6H), 2.09 (d, J = 16.1 Hz, 2H), 2.27 (d, J = 16.2 Hz, 2H), 2.53 (d, J = 17.1 Hz, 2H), 2.58 (d, J = 17.7 Hz, 2H), 4.53 (s, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.18 (d, J = 7.0 Hz, 2H), 7.21 (t, J = 7.20 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 27.7, 29.6, 32.3, 32.6, 41.3, 51.2, 116.1, 126.8, 128.4, 128.8, 144.5, 162.7, 196.8.

3,3,6,6-Tetramethyl-9(4-chloro-Phenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 2)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (s, 6H), 1.04 (s, 6H), 2.09 (d, J = 16.1 Hz, 2H), 2.27 (d, J = 16.1 Hz, 2H), 2.52 (d, 2H), 2.57 (d, J = 17.6 Hz, 2H), 4.51 (s, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl^3$, 125 MHz): 27.7, 29.7, 31.8, 32.6, 41.3, 51.1, 115.6, 128.6, 130.2, 132.4, 143.1, 162.8, 196.7.

3,3,6,6-Tetramethyl-9(3-nitro-Phenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 6)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.91 (s, 6H), 1.04 (s, 6H), 2.11 (d, J = 16.1 Hz, 2H), 2.29 (d, J = 16.1 Hz, 2H), 2.57 (d, J = 17.9 Hz, 2H), 2.60 (d, J = 17.9 Hz, 2H), 4.65 (s, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 8.00 (d, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 27.2, 29.6, 32.0, 32.7, 50.9, 56.6, 60.7, 106.3, 115.1, 136.8, 140.7, 153.2, 163.9, 197.0

Results and Discussion

Initially, we studied effect of amount of the catalysts on the reaction of dimedone (2 mmol) with benzaldehyde (1 mmol) at 55-60 °C. The results are summarized in Table 1. As it can be seen in Table 1, the best amounts of TUD aqueous solution was 2%.

Table 1. Synthesis of 3,3,6,6-Tetramethyl-9(phenyl)-1,8-dioxo-octahydroxanthene

S. No.	% of TUD aqueous solution	Time in Min	Yield %
1	10	45	92
2	5	45	92
3	2	45	96
4	1	70	80

After optimization of the reaction conditions, dimedone was reacted with different types of aldehydes (including aromatic aldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings) in the presence of the thiourea dioxide as catalysts. The results are displayed in Table 2. As it is shown in Table 2, all reactions were completed within 35-50 min and the desired products were obtained in good to excellent yields (82-97%). Thus, our method is highly efficient and general.

Table 2. Synthesis of 1,8-dioxo-octahydroxanthenes using TUD as catalyst

Entry	R	Time in Min	Yield [a] %	M.P. °C
1	C_6H_5	45	96	200-202
2	*p*-ClC_6H_4	35	97	230-232
3	*m*-ClC_6H_4	35	90	184-186
4	*o*-ClC_6H_4	40	91	224-226
5	*p*-$NO_2C_6H_4$	40	97	222-224
6	*m*-$NO_2C_6H_4$	30	94	162-164
7	*o*-$NO_2C_6H_4$	50	88	250-252
8	*p*-Br C_6H_4	40	92	240-242
9	*o*-BrC_6H_4	40	83	226-228
10	*p*-CNC_6H_4	45	82	218-220
11	*p*-$CH_3C_6H_4$	40	94	214-216
12	*m*-$CH_3C_6H_4$	35	94	208-210
13	*o*-$CH_3C_6H_4$	50	84	210-212
14	*p*-$CH_3OC_6H_4$	45	89	242-244
15	*m*-$CH_3OC_6H_4$	50	85	160-162

[a]*Isolated yields*

Conclusion

We have developed a new method for the synthesis of 1,8-dioxoocta-hydroxanthenes using TUD in aqueous media as catalyst. The simple experimental and work-up procedure, high yields, relatively short reaction times, application of inexpensive catalyst and compliance with the green chemistry protocols are the advantages of the present method.

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References

1. Hideo T, Tokkyo Koho J P 56005480, 1981, *Chem Abstr.*, 1981, **95,** 80922b, Jpn.
2. Lambert R W, Martin J A, Merrett J H, Parkes K E B and Thomas G J, *PCT Int Appl.*,WO9706178, 1997, *Chem Abstr.*, 1997, **126,** p212377y.
3. Poupelin J P, Saint-Rut G, Fussard-Blanpin O, Narcisse G, Uchida-Ernouf G and Lakroix R, *Eur J Med Chem.*, 1978, **13**, 67-71.
4. Chibale K, Visser M, Schalkwyk D V, Smith P J, Saravanamuthu A and Fairlamb A H, *Tetrahedron*, 2003, **59(13)**, 2289-2296; DOI:10.1016/S0040-4020(03)00240-0
5. (a) Hatakeyma S, Ochi N, Numata H and Takano S, *J Chem Soc Chem Commun.*, 1988, 1202-1204; DOI:10.1039/C39880001202 (b) Cingolant G, Fulvio G and Pigini M, *J Med Chem.*, 1969, **12**, 531-532; DOI:10.1021/jm00303a616
6. (a) Arnone A, Merlini L and Nasini G, *Tetrahedron Lett.*, 1972, **13(33)**, 3503-3506; DOI:10.1016/S0040-4039(01)94083-3 (b) Ravindranath B and Sheshadri T R, *Phytochemistry*, 1973, **12(11)**, 2781-2788; DOI:10.1016/0031-9422(73)85099-X (c) Kinjo J, Uemura H, Nohara T, Yamashita M, Marubayashi N and Yoshihira K, *Tetrahedron Lett.*, 1995**, 36(31)**, 5599-5602; DOI:10.1016/0040-4039(95)01071-O
7. Banerjee A and Mukherjee A K, *Stain Technol.*, 1981, **56(2)**, 83-85.
8. (a) Menchen S M, Benson S C, Lam J Y L, Zhen W, Sun D, Rosenblum B B, Khan S H and Taing M, U.S. Patent, US6583168, 2003, *Chem Abstr*., 2003, **139**, p54287f; (b) Sirkecioglu O, Tulinli N and Akar A, *J Chem Res (S)*, 1995, 502-506.
9. (a) Bekaert A, Andrieux J and Plat M, *Tetrahedron Lett.*, 1992, **33(20)**, 2805-2806; DOI:10.1016/S0040-4039(00)78863-0 (b) Sarma R J and Baruah J B, *Dyes Pigm.*, 2005, **64(1)**, 91-92; DOI:10.1016/j.dyepig.2004.03.010 (c) Buehler C A, Cooper D E and Scrudder E O, *J Org Chem.*, 1943, **8(4)**, 316-319; DOI:10.1021/jo01192a003 (d) Knight C G and Stephens T, *Biochem J.*, 1989, **258(3)**, 683-687.
10. (a) Ion R M, Frackowiak D, Planner A and Wiktorowicz K, *Acta Biochim Pol.*, 1998, **45(3)**, 833-845; (b) Ion R M, *Prog Catal.*, 1997, **6**, 55.
11. (a) Hamada Y, Matsuura F, Oku M, Hatano K and Shioiri T, *Tetrahedron Lett.*, 1997, **38(52)**, 8961-8964; DOI:10.1016/S0040-4039(97)10363-X (b) Hillebrand S, Bruckmann J, Kruger C and Haenel M W, *Tetrahedron Lett.*, 1995, **36(1)**, 75-78; DOI:10.1016/0040-4039(94)02206-Q (c) Malaise G, Barloy L and Osborn J A, *Tetrahedron Lett.*, 2001, **42(42)**, 7417-7419; DOI:10.1016/S0040-4039(01)01588-X
12. Kuthan J, Sebek P and Bohm S, Advances in Heterocyclic Chemistry; Academic Press lnc: New York, 1995,**62**, 19.
13. (a) Horning E C and Horning M G, *J Org Chem.*, 1946, **11(1)**, 95-99; DOI:10.1021/jo01171a014 (b) Tu S J, Zhou J F, Lu Z S, Deng X, Shi D Q and Wang S H, *Synth Commun.*, 2002, **32(19)**, 3063-3067; DOI:10.1081/SCC-120012999

(c) Jin, T S, Zhang J S, Wang A Q and Li T S, *Synth Commun.*, 2005, **35(17)**, 2339-2345; DOI:10.1080/00397910500187282

14. Wang X S, Shi D Q, Li Y L, Chen H, Wei X Y and Zong Z M, *Synth Commun.*, 2005, **35(1)**, 97-104; DOI:10.1081/SCC-200046510
15. Jin T S, Zhang J S, Xiao J C, Wang A Q and Li T S, *Synlett.*, 2004, 866-870; DOI:10.1055/s-2004-820022
16. Darvish F, Balalaei S, Chadegani F and Salehi P, *Synth Commun.*, 2007, **37**, 1059-1066; DOI:10.1080/00397910701196520
17. Jin T S, Zhang J S, Wang A Q and Li T S, *Ultrason Sonochem.*, 2006, **13(3)**, 220-224; DOI:10.1016/j.ultsonch.2005.04.002
18. Dabiri M, Baghbanzadeh M and Arzroomchilar E, *Catal Commun.*, 2008, **9(5)**, 939-942; DOI:10.1016/j.catcom.2007.09.023
19. Das B, Thirupathi P, Mahender I, Reddy V S and Rao Y K, *J Mol Catal A Chem.*, 2006, **247(1-2),** 233-239; DOI:10.1016/j.molcata.2005.11.048
20. Das B, Thirupathi P, Mahender I, Reddy K R, Ravikanth B and Nagarapu L, *Catal Commun.*, 2007, **8(3)**, 535-538; DOI:10.1016/j.catcom.2006.02.023
21. Srihari P, Mandal S S, Reddy J S S, Srinivasa Rao R and Yadav J S, *Chin Chem Lett.*, 2008, **19(7)**, 771-774;DOI:10.1016/j.cclet.2008.05.005
22. Rostamizadeh S, Amani A M, Mahdavinia G H, Amiri G and Sepehrian H, *Ultrason Sonochem.*, 2010, **17(12)**, 306-309; DOI:10.1016/j.ultsonch.2009.10.004
23. Mahdavi G H, Bigdeli M A and Saeidi Hayeniaz Y, *Chin Chem Lett.*, 2009, **20(5)**, 539-541; DOI:10.1016/j.cclet.2008.12.026
24. Imani Shakibaei G, Mirzaei P and Bazgir A, *Appl Catal A: General*, 2007, **325(1)**, 188-192; DOI:10.1016/j.apcata.2007.03.008
25. Kantevari S, Bantu R and Nagarapu L, *J Mol Catal A: Chem.*, 2007, **269(1-2)**, 53-57; DOI:10.1016/j.molcata.2006.12.039
26. Maghsoodlou M T, Habibi-Khorassani S M, Shahkarami Z, Maleki N and Rostamizadeh M, *Chin Chem Lett.*, 2010, **21(6)**, 686-689; DOI:10.1016/j.cclet.2010.02.005
27. Karthikeyan G and Pandurangan A, *J Mol Catal A: Chem.*, 2009, **311(1-2)**, 36-45; DOI:10.1016/j.molcata.2009.06.020
28. Ohura O and Fujimoto O, U.S. Patent 4, 233,238, 1980.
29. S.Verma, S. L. Jain and B. Sain, *Tetrahedron Lett.*, 2010, **51(52)**, 6897–6900; DOI:10.1016/j.tetlet.2010.10.124