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Microwave assisted synthetic approach for 1, 8-dioxo- octahydroxanthene derivatives under solvent free condition

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Abstract: A simple, efficient and rapid protocol for the synthesis of 1, 8-dioxo-octahydroxanthenes under microwave irradiation by using etidronic acid as homogeneous catalyst with simple methodology, easy workup procedure (without any chromatographic separation) and excellent yield. This protocol offers several merits like mild reaction conditions, environmentally friendly reaction, shorter reaction time.

Keywords: Microwave Irradiation, Etidronic acid, Xanthene derivatives.

Introduction

Recently in the synthetic organic chemistry, as concern with the today's urgent need of energy management, it is necessary to use low energy consuming methodology for any targeted synthetic intermediates and/or molecules. Among the all other existing processes, microwave irradiation is one of the method which is very versatile because of many organic reactions like substitution, cycloaddition etc. are assisted by microwave irradiation for reducing reaction time, increasing product yield, use of less or no solvent, enhancing product purity and reducing unwanted side products as compared to the conventional methods.

Different reactions were carried out by microwave irradiation like hydration of aryl acetylenes [1], synthesis of fused piperazine-benzimidazoles [2], 10b-aza-10c-borapyrene [3], direct esterification of cyclic phosphonic acids [4], sonogashira-type coupling [5], synthesis of polyfunctional 1,3-dioxolanes [6], etc. By considering these versatile application, now a day's researchers use this technique as an alternative for traditional methods.

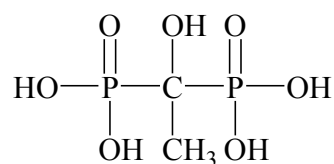
Because of the pharmaceutical and biological properties, xanthene derivatives have attracted considerable attention in recent years. Among the heterocyclic family, compounds having xanthene as a core moiety

has biological properties like anticancer, analgesic, anti-inflammatory, antibacterial [7-10], anti-depressants and antimalarial agents [11], u-opiant [12], antitumor [13], neuropharmacological [14], CNS stimulating [15], antioxidant [16]. Moreover, along with these properties this core moiety has been used as dyes [17], pH-sensitive fluorescent materials for the visualization of bio-molecular assemblies [18], sensitizers in photodynamic therapy [19]. Besides this these compounds found as an agricultural bactericidal activity [20]. Hence by considering these significance there are different methods for the synthesis of xanthene derivatives

Among the reported different methods for the synthesis of xanthene derivatives, most commonly used method is by condensation of aldehydes with 1, 3-cyclohexanedione or 5, 5-dimethyl-1, 3-cyclohexanedione. For this conversion different catalysts are used like, alumina-sulfuric acid [21], NaHSO₄-SiO₂ [22], ZnO-acetyl chloride [23], PMA-SiO₂ [24], NBS [25], ZrOCl₂·8H₂O [26], trichloroisocyanuric acid [27], silica sulfuric acid [28], heteropolyacid supported MCM-41 [29], silica bonded N-propyl sulfamic acid [30], nanosized MCM-41-SO₃H, [31] [Bmim][HSO₄], [32] [Hmim] TFA, [33] [TMPSA]HSO₄, [34] [DDPA][HSO₄] [35], [Et₃N-SO₃H]Cl [36], and [Hbim]BF₄ [37]. More recently, this condensation was carried by using carbon nanostructures based catalytic systems like graphene oxide, sulfated graphene nanosheets [38] and Ru-MWNTs [39]. In addition to this, FeCl₃·6H₂O used as a catalyst for the synthesis of 1-oxo-hexahydroxanthenes by the condensation of salicylaldehydes with 1,3-diketones [40]. However, most of the existing methods having some merits and demerits like use of hazardous organic solvents, longer reaction time and tedious workup procedure. Hence there is an urgent need to develop novel protocol for easy isolation of product, environmentally benign catalyst, less

reaction time, use of non-conventional energy source etc.

Etidronic acid (1-hydroxyethane-1,1-diphosphonic acid) is an organophosphonic acid, containing C-P(O)(OH₂) groups which are characterized by a stable, covalent C-P bond. It can be treated as a complexing agent. HEDP is water soluble, chemically stable under high pH, hard hydrolyzed and hard decomposed under light exposition and heat condition.



Etidronic acid

As per literature survey very few reports are there for etidronic acid used in organic synthesis as a catalyst. Y.T. Naliapara et.al. synthesise 5-nitro-3,4-dihydropyrimidin-2(1H)-ones [41], 5-carboxymethylated-dihydropyrimidinones [42] and trifluoromethylated tetrahydropyrimidines [43] using etidronic acid as a catalyst. While B. Madje et.al. used etidronic acid as catalyst for knoevenagel condensation of 4-oxo-4H-benzopyran-3-carbaldehyde with meldrum acid [44]. This literature data encourage us to use etidronic acid for our present methodology.

Materials and methods

All chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light. Melting points were recorded in open capillary tubes and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 500 MHz and Bruker DRX 100 MHz spectrometer respectively.

Experimental

Typical Procedure for the preparation of 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8(5H,9H)-dione (3a):

To a mixture of benzaldehyde (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (2 mmol) add etidronic acid (10 mol%) and irradiated in microwave synthesizer for appropriate time. After completion of reaction, the reaction mixture was poured on a crushed ice and filtered off the crude product. The crude product was recrystallized from appropriate solvent.

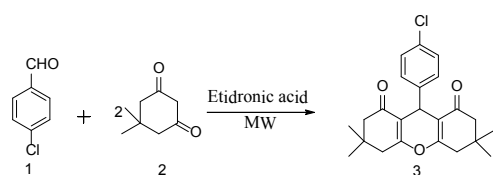
Characterization of representative compound.

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8(5H,9H)-dione(3c):

¹HNMR (500 MHz, CDCl₃): δ (ppm) 0.99 (s, 6H, 2 -CH₃), 1.12 (s, 6H, 2 -CH₃), 2.50-2.59 (m, 8H, 4 -CH₂), 4.65 (s, 1H), 7.18-7.21 (m, 4H). ¹³C NMR: δ (ppm) 27.3, 29.2, 31.8, 32.2, 40.8, 50, 7, 115.6, 126.3, 128.0, 128.3, 144.1, 162.2, 196.4 MS, m/z(%): 385(M +1)

Result and Discussion

In search of the best experimental reaction conditions for the preparation of 1,8-dioxo-octahydroxanthenes, reaction of p-chlorobenzaldehyde (1 mmol) and dimedone (2 mmol) in the presence of etidronic acid as a catalyst was selected as model reaction (Scheme 1).



Scheme 1:- Standard Model Reaction

To evaluate the effect of solvents, model reaction was performed in different solvents

like acetonitrile, ethanol, chloroform, THF, DMF and solvent free condition to achieve the targeted compounds. Surprisingly, we observed that under solvent free condition the desired product was obtained in better yield (82 %). Other solvents like acetonitrile, ethanol, chloroform, THF and DMF was afforded poor yield. (i.e. 55, 30, 35, 60 and 50 % respectively). So the reaction was performed under solvent free condition.

Table 1:- Screening of Solvent

Entry	Catalyst	Mol% of catalyst	Solvent	^b Yield (%)
1	Etidronic acid	5	Neat	82
2	Etidronic acid	5	Acetonitrile	55
3	Etidronic acid	5	Ethanol	30
4	Etidronic acid	5	Chloroform	35
5	Etidronic acid	5	THF	60
6	Etidronic acid	5	DMF	50

^aReaction condition: p-chlorobenzaldehyde (1 mmol), dimedone (2 mmol), catalyst etidronic acid, microwave irradiation ^bIsolated yields.

To determine the appropriate concentration of the catalyst, the model reaction was investigated at different catalyst loading such as 0, 1, 5, 10, 15 and 20 mol % which offered 45, 62, 82, 95, 93 and 93 % product yields respectively (Table 2). This indicates that 10 mol% of etidronic acid was enough to carry out the reaction efficiently with excellent yield. Further, there was no significant enhancement in the yield at higher concentration i.e. 15 mol% and 20 mol%. Hence, 10 mol% of the catalyst was sufficient to afford the desired product in excellent yield.

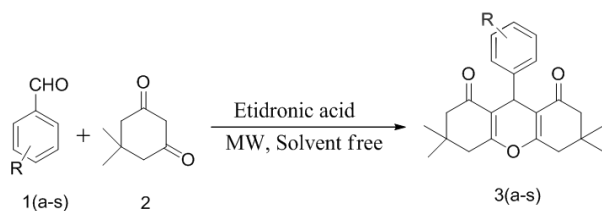
Table 2:-Screening of catalyst concentration under microwave irradiation.

Entry	Mol % of catalyst	Time (min)	Yield (%) ^b
1	0	15	45
2	1	10	62
3	5	10	82
4	10	05	95
5	15	05	93
6	20	05	93

^a**Reaction condition:** p-chlorobenzaldehyde (1mmol), dimedone (2mmol), catalyst etidronic acid, Microwave irradiation ^bIsolated yields.

To explore the scope of this reaction, a series of aryl and heterocyclic aldehydes were allowed to react with dimedone under identical conditions. Both the electron-rich and the electron deficient aryl aldehydes showed an excellent reactivity and furnished the products in high yields in short reaction times (**Table 3, entries 1–19**). There was no significant affect on the product yield while using both the electron-rich and the electron deficient aryl and heterocyclic aldehydes. The ability to operate for a range of substrates at low catalyst loading is of great importance in catalysis processes. Thus, our present result is quite significant as the desired cyclocondensation could be achieved. Moreover, their MPs. is in good agreement with the previous reports.

Synthesis of 1,8-dioxo-octahydroxanthene

**Table :- 3**

Entry	R	Product	Time (min)	Melting Point (°C)		Yield (%) ^b
				Reported	Found	
1)	-H	3a	3-5	201-202	202-204	90
2)	4-methyl	3b	3-5	216-217	215-216	89
3)	4-chloro	3c	3-5	230-232	231-232	95
4)	4-methoxy	3d	3-5	242-244	239-240	88
5)	4-fluro	3e	3-5	226-227	225-226	89
6)	4-bromo	3f	3-5	240-241	239-241	89
7)	4-nitro	3g	3-5	225-227	223-226	89
8)	2-chloro	3h	3-5	225-227	225-228	90
9)	2-hydroxy	3i	3-5	202-205	200-204	89
10)	2-bromo	3j	3-5	226-229	226-228	89
11)	2-nitro	3k	3-5	258-262	259-260	88
12)	3-nitro	3l	3-5	166-168	169-170	90
13)	3-hydroxy	3m	3-5	223-225	220-222	89
14)	3-bromo	3n	3-5	190-192	190-191	88
15)	4-hydroxy	3o	3-5	248-250	247-249	89
16)	4-hydroxy-3-methoxy	3p	3-5	226-228	224-227	89
17)	3-methoxy	3q	3-5	163-164	161-162	90
18)	2-thienyl	3r	3-5	164-165	163-164	83
19)	2-furyl	3s	3-5	62-64	61-62	85

^a**Reaction condition:** p-chlorobenzaldehyde (1mmol), dimedone (2mmol), catalyst etidronic acid (10 mol %) microwave irradiation ^bIsolated yields.

Conclusion-

In conclusion, the present protocol offers mild and efficient synthetic method for the preparation of 1,8-dioxo-octahydroxanthene derivatives using etidronic acid as a catalyst under microwave irradiation with high yield, short reaction time, easy product isolation with simple workup procedure.

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