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SYNTHESIS AND BIOLOGICAL ACTIVITY OF TETRAMETHYL-HEXAHYDRO-1*H*-XANTHENE-1,8(2*H*)-DIONEDERIVATIVES

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Abstract:
Tetramethyl-hexahydro-1*H*-xanthene-1,8(2*H*)-dione Derivatives (3a-e) have been synthesized by thecondensation of two moles of Dimedone and substituted Aromatic aldehydesin ethanol-water mixture using Tetra Butyl Ammonium Hydrogen Sulphate (TBAHS) as a green catalyst. The products have been assayed for their antimicrobial screening against Gram+ve and Gram-ve bacteria. Some of the products showed moderate activity when compared with known standard drug viz. penicillin at the same concentration 10µgm/ml. Spectroscopic technique are very good tools for the identification of compounds. The structures have been confirmed by 1H NMR,^{13}C-NMR, IR, and Massspectral data.

Keywords: Dimedone, Aromatic aldehydes, TBAHS, Antimicrobialscreening

Introduction:

Xanthenes derivatives are the parent skeleton found in a large number of natural products as well as synthetic products possessing prominent positions in medicinal chemistry.[i] Because of their wide range of synthetic, industrial and pharmacological application. Xanthene derivatives are very important heterocyclic compounds and have been widely used as dyes[ii] and fluorescent materials for visualization of biomolecules and in laser technique[iii]. They have also been reported for their anti-inflammatory[iv], antiviral activity[v] and agricultural bactericide activity[vi]. Xanthenediones are synthesized by many procedures one among the conventional methods involves acid or base-catalyzed condensation of appropriate active methylene carbonyl compounds with aldehydes[vii].

Various methods for the synthesis of xanthenes are described in the literature including condensation of aromatic aldehydes and dimedone using silica sulfuric acid[viii]. $FeCl_3.6H_2O$[ix], $NaHSO_4.SiO_2$[x], TiO_2/SO_4[xi], $InCl_3.4H_2O$[xii], Dowex-50W[xiii], $ZrOCl_2.8H_2O$[xiv], Alumina-sulfuric acid[xv], Fe^{3+}-montmorillonite[xvi] and amberlyst-15 catalyst[xvii] as solid acid catalysts have been

proposed. In addition, the synthesis of other xanthene-dione derivatives over HPA/SiO_2[xviii], preyssler type heteropoly acid[xix] and HPWA/ MCM-41[xx] has been reported.

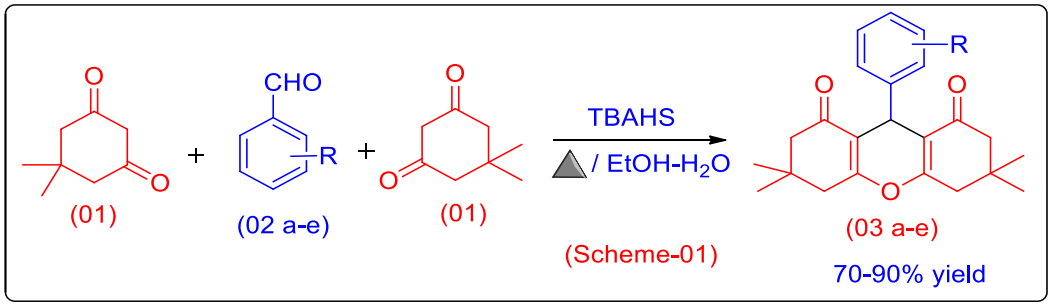
Materials and Methods:

All the chemicals were obtained from Sigma Aldrich and Thomas Baker. These chemicals were applied without extra purification procedures. The reactions were carried out in dried glassware. The chemicals of analytical grade were procured from commercial sources and used as such without further purification. Open capillary tubes were used for melting points of isolated synthesized compounds and are uncorrected. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of compounds. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on spectrometer at 400MHz using TMS as an internal standard.

General procedure for the synthesis of tetramethyl-hexahydro-1*H*-xanthene-1,8(2*H*)-dione Derivatives(03a-e):

A mixture of two moles of Dimedone and substituted Aromatic aldehydeswas refluxedin ethanol-water mixture using Tetra Butyl Ammonium Hydrogen Sulphate (TBAHS) as a green catalyst for period of time to afford the respective products. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid was filtered and purified from DMF:water (80:20)and recrystallized by ethanol to give **(03a-e)**.The yield of products is between 75-90 %.The reaction was monitored by TLC. These synthesized compounds were completely characterized from IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic technique and also elemental analysis.

Result and Discussion:



(Scheme-01)

We initially focused on optimization of the reaction condition. The reaction mixture of two moles of Dimedone and substituted Aromatic aldehydes was refluxed in ethanol-water mixture using Tetra Butyl Ammonium Hydrogen Sulphate (TBAHS) as a green catalyst, It was considered as a model reaction (**Scheme-01**) for investigating the effectiveness of different polar and non polar solvent using catalytic amount of TBAHS15 mmol %. Solvent optimization clearly noted that ethanol-water is the best solvent for the desired transformation due to fast reaction rate and high yield (Table-1, entry 6). The other polar protic solvents gives moderate yield (Table-1, entry 5), while other aprotic solvent like Acetonitrile,DCM, DMF, THFdisplayed slow reaction rates leading lower yield (Table-1, entry 1-4). We have carried out the model reaction using different stoichiometric amount of catalyst. The catalyst screening result are summarized in Table-2. It was observed that the excellent yield was achieved by using of TBAHS 15 mole % (Table-2, entry 6).

Further investigating the influence of different parameters on the model reaction, we turned our attention towards the tetramethyl-hexahydro-1*H*-xanthene-1, 8(2*H*)-dione Derivatives**(03a-e)** using reaction of Dimedone **(01)**and different substituted aromatic aldehydes **(02a-e)**, was refluxed independently in ethanol-water using TBAHS15mole %and

the result are summarized in Table-3. With the both electron-poor and electron-rich benzaldhydes (Table-3, entries 1-5), the corresponding tetramethyl-hexahydro-1*H*-xanthene-1, 8(2*H*)-dione Derivatives**(03a-e),** were obtained to excellent yields. These synthesized products **(03a-e)** were characterized from IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic technique and elemental analysis.

Table-1: Optimization of the reaction conditions using different solvents[a]

Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	Acetonitrile	5.0	45
2	DCM	5.0	48
3	DMF	5.0	55
4	THF	5.0	60
5	Ethylene glycol	5.0	70
6	Ethanol-water	5.0	88

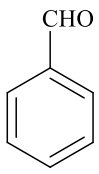
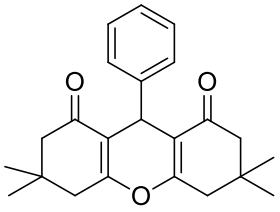
[a]*Reaction conditions:**Dimedone(10 mmol)andAromaticaldehyde (10 mmol) was refluxed.*
[b] *Isolated yields.*

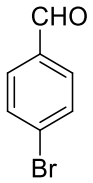
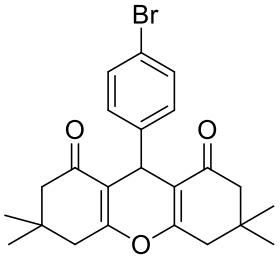
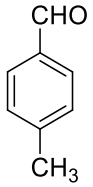
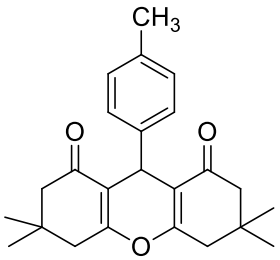
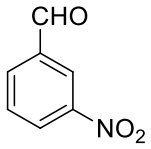
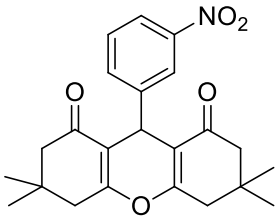
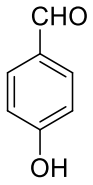
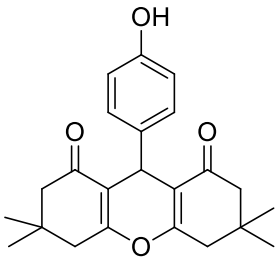
Table 2: Optimization Study for the amount TBAHS[a]

Entry	Catalyst (mole %)	Temperature (^{0}C)	Reaction Time (h)	Yield %[b]
1	01	90	4.0	45
2	02	90	4.0	50
3	05	90	4.0	55
4	08	90	4.0	60
5	10	90	4.0	70
6	15	90	4.0	90
7	20	90	4.0	90

[a]*Reaction conditions:* *Dimedone(10 mmol) and Aromatic aldehyde (10 mmol) was refluxed.*
[b] *Isolated yields.*

Table 3: Reaction of *Dimedone*andAromaticaldehydefor the synthesis of **(03a-e)[a]**

Entry	Aldehyde (02a-e)	Products (03 a-e)	Time (h)	Yield (%)[b]	M.P. (^{0}C)
1		 **3a**	4.0	75	203-206

2		 **3b**	4.0	85	240-242
3		 **3c**	4.0	90	210-212
4		 **3d**	4.0	80	190-192
5		 **3e**	4.0	86	250-252

[a]*Reaction conditions:* (01) (10 mmol), (02) (10 mmol) and ethanol in TBAHS 15 mole % were refluxed.
[b] Isolated yield

Spectral Analysis:

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (03a):
M.P. 203-206^{0}C; Yield 75%; IR (KBr, *v*max, cm^{-1}) 3010, 2930, 1643, 1566, 1364,1257; ^{1}H NMR (400MHz, DMSO-d$_6$,ppm)δ 1.10 (s, 6H, 2CH$_3$), δ 1. 25(s, 6H, 2CH$_3$), δ2.09-2.57 (m, 8H, 4CH$_2$),δ 4.56 (s, 1H, CH), δ7.15-7.45 (m, 5H, Ar-H);^{13}C NMR (400 MHz, DMSO–d$_6$, ppm): *δ* 195.7, 162.4, 144.2, 139.6.9, 128.1, 127.8, 127.6, 127.1, 126.4,126.0,125.1, 114.7, 50.3,46.5, 40.3, 40.1, 39.9, 39.7, 31.8, 26.7; EI-MS (m/z: RA %): 350 (M$^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{23}H_{26}O_3$; C, 78.83; H, 7.47; Found: C, 78.85; H, 7.45.

9-(3-Bromo-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (03b):
M.P. 240-242^{0}C; Yield 85%; IR (KBr, *v*max, cm^{-1}) 3380, 2923, 1647, 1566, 1373, 1157; ^{1}H NMR (400MHz, DMSO-d$_6$,ppm),δ 0.94 (s, 6H, 2CH$_3$), δ 1.08(s, 6H, 2CH$_3$), δ 2.06-2.56 (m,

8H, 4CH_2), δ 4.67 (s, 1H, CH), δ7.52(d, 2H, Ar-H), δ8.03(d, 2H, Ar-H); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): *δ* 195.7, 162.4, 143.5, 130.6., 130.5, 130.2, 128.6, 119.4, 114.2, 50.3, 46.4, 40.3, 40.1, 39.2, 39.0, 31.4, 26.8; EI-MS (m/z: RA %): 429 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{23}H_{25}BrO_3$; C, 64.34; H, 5.87; Found: C, 64.30; H, 5.90.

3,3,6,6-Tetramethyl-9-p-tolyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (03c):

M.P. 210-212^{0}C; Yield 90%; IR (KBr, *ν*max, cm^{-1}) 2931, 1660, 1580, 1315, 1137; ^{1}H NMR (400MHz, DMSO-d_6,ppm), δ 0.92 (s, 6H, 2CH_3), δ 1.05(s, 6H, 2CH_3), δ 2.05-2.56 (m, 8H, 4CH_2),δ 2.25 (s, 3H, CH_3), δ 4.49 (s, 1H, CH), δ 6.97(d, 2H, Ar-H), δ 7.07(d, 2H, Ar-H); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): *δ* 195.7, 162.3, 155.7, 141.2., 134.9, 128.2, 127.9, 114.4, 50.1, 40.1, 39.4, 39.1, 30.4, 26.5; EI-MS (m/z: RA %): 364 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{24}H_{28}O_3$; C, 79.08; H, 7.74; Found: C, 79.10; H, 7.72.

3,3,6,6-Tetramethyl-9-(3-nitro-phenyl)-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione(03d):

M.P. 190-192^{0}C; Yield 80%; IR (KBr, *ν*max, cm^{-1}) 3110,2958, 1631, 1566, 1346, 1149; ^{1}H NMR (400MHz, DMSO-d_6,ppm), δ 0.98 (s, 6H, 2CH_3), δ 1.08(s, 6H, 2CH_3), δ 2.09-2.57 (m, 8H, 4CH_2),δ 4.67 (s, 1H, CH), δ 7.48-8.03(m, 4H, Ar-H); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): *δ* 195.8, 163.1, 147.3, 146.2, 134.5, 129.0, 122.7, 121.1, 113.4, 49.9, 40.2, 39.9, 39.1, 31.8, 26.6; EI-MS (m/z: RA %): 395 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{23}H_{25}NO_5$; C, 69.08; H, 6.37; Found: C, 69.10; H, 6.35.

9-(4-Hydroxy-phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione (03e):

M.P. 250-252^{0}C; Yield 86%; IR (KBr, *ν*max, cm^{-1}) 3412, 2988, 16508, 1550, 1335, 1146; ^{1}H NMR (400MHz, DMSO-d_6,ppm), δ 0.96 (s, 6H, 2CH_3), δ 1.12(s, 6H, 2CH_3), δ 2.20-2.50 (m, 8H, 4CH_2), δ 4.75 (s, 1H, CH), δ 5.20 (s, 1H, OH), δ 6.90(d, 2H, Ar-H), δ 7.25(d, 2H, Ar-H); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): *δ* 195.5, 162.3, 142.5, 145.1, 139.5, 135.2, 123.6, 122.9, 114.5, 40.7, 40.6, 39.8, 39.0, 32.2, 26.4; EI-MS (m/z: RA %): 366 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{23}H_{26}O_4$; C, 75.38; H, 7.15; Found: C, 75.10; H, 7.45.

Antimicrobial Activity:

We have used the *Agar* well diffusion method for assessment of the antimicrobial activity of newly synthesized compounds. On Muller-Hinton agar medium zone of inhibition were observed and zone diameter was recorded in mm against specific test microorganisms.

The synthesized compounds were accessed antimicrobial activity particularly antibacterial and antifungal. The antibacterial activity against Gram positive Staphylococcus aureus bacteria and Gram negative bacteria are Escherichia coli, Proteus vulgarisusing standard drugs are Penicillin and Streptomycin. The antifungal activity screened against Aspergillusfumigatus, Aspergillusniger using Nystatin as standard drug.

The synthesized compounds **03b,03c and 03e**showed good antibacterial activity against **Staphylococcus aureus** as compaired to standard drugs Penicillin and Streptomycin. The compounds **03a, 03band 03d**showed good antibacterial activity against **Escherichia colias** compaired to standard drugs Penicillin and Streptomycin. The synthesized compounds **03b, 03c and 03d**showed good zone of inhibition against **Proteus vulgaris** as compaired to Penicillin and Streptomycin.

The synthesized compounds **03b, 03c and 03e**showed good zone of inhibition against **Aspergillusfumigatus** as compaired to Nystatin. The synthesized compounds **03a, 03c and 03d**shows good zone of inhibition against **Aspergillusniger** as compaired to Nystatin.

Table 4: Antimicrobial activity of tested compounds (03a-e).

Sr.No.	**Compounds**	**Zone of inhibition* (mm)**				
		Bacterial Species			**Fungal Species**	
		Gram positive	**Gram negative**		***Aspergillusfumigatus***	***Aspergillusniger***
		Staphylococcus aureus	***Escherichia coli***	***Proteus vulgaris***		
01	**03a**	10	16	ND	10	18
02	**03b**	16	18	18	14	ND
03	**03c**	18	10	16	18	20
03	**03d**	12	18	16	10	18
05	**03e**	20	ND	10	20	14
Ref*	Penicillin	26 mm	40 mm	18 mm	-----	-----
	Streptomycin	40 mm	35 mm	34 mm	----	-----
	Nystatin (10 µgm/ml)	-----	-----	-----	40 mm	28 mm

ND= Not detected zone of inhibition under experimental condition.

Conclusion:

We have developed an operationally simple, eco-friendly,inexpensive and efficient, synthesis of tetramethyl-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives. The procedure offers several advantages including improved yields, cleaner reactions and low cost which makes it a useful and attractive strategy in view of economic and environmental advantages. Furthermore these compounds were evaluated for their antibacterial activity. Some of the compounds showed good activity against gram positive and gram negative bacterial strains.

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