Facile and An Efficient Synthesis of Bis-Trifluoromethyl 1, 8-Dioxo-Octahydroxanthene Promoted by $ZrOCl_28H_2O$

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Abstract: Xanthenedione are structural components of several bioactive and semi-synthetic molecules. This work described an expeditious synthesis of novel and hither to unreported Bis-Trifluoromethyl xanthenedione analogous. The reaction of two equivalents of 5-trifluoromethyl cyclohexane-1, 3-dione with substituted aromatic aldehydes in the presence of ethanol containing $ZrOCl_28H_2O$ was facile under reflux. Short reaction time (5hrs), good to excellent yields (85% - 95%), good atom economy, and simple workup are the major advantages of the above procedure. The structure of these compounds has been confirmed on the basis of their advanced spectroscopic data ^{1}HNMR, ^{13}CNMR and LCMS spectral data and also structural determination was calculated by elemental analysis.

Keywords: Xanthenedione, substituted aromatic aldehyde, 5-(Trifluoromethyl) cyclohexane-1, 3-Dione, $ZrOCl_28H_2O$.

1. INTRODUCTION

Among various reports were evidenced that submitted of 9-phenyl substituted xanthenedione derivatives possessing bis-methyl, ethyl, isopropyl, phenyl and hydrogen have appeared in the literature [1] [2] [3] [4], the corresponding Bis-Trifluoromethyl group have received little or no attention. The various derivatives having the fore mentioned substituents exhibited a wide range of biological properties, such as antidepressant [5], anticholinesterase [6] and anti-cancer [7] [8] activities. The biological activities were evidenced to depend on the nature of the moiety present at the 9-position of the central pyranring. The introduction of a phenyl sulphonamide at the above position gave rise to derivatives with antimicrobial [9] [10], antimalarial [11][12], and antibacterial activities [13] [14] [15] [16]. The replacement of the sulphonamide with a carboxamidegener with a carboxamide generated derivatives as those of sulphonamide but also displayed fungicidal activity [17]. Fluorine atoms attached to organic molecules exhibit "polar hydrophobicity" as described by DiMaggio [18] [19] [20] [21] [22]. The above behaviour appears to cause the fluoro-alkyl groups to participate in less dispersive interaction with aqueous solvent. Thus, the above property could in part explain the enhanced fluorine-containing small organic molecule binding affinity to a putative protein target.

The most of the literature survey submitted that a typical procedure for the synthesis and their 1, 8-dioxo derivatives involved the well-known one pot multicomponent reaction of a cyclic β-diketone with substituted aromatic aldehydes under a different condition of reaction conditions. The reported reaction conditions included use of protonic acids [23], Lewis acids ($InCl_3{\cdot}4H_2O$ [24], $FeCl_3{\cdot}6H_2O$ [25], and $NaHSO_4$ [26]). In other hand, Dowex-50W,[27] and $NaHSO_4{\cdot}SiO_2$, [28] are heterogeneous catalyst were reported. Unfortunately, so many of the above reported methods suffer from a number of drawbacks, such as use of hazardous solvent, prolonged reaction conditions, tedious workup procedure low yields of products and use of excess catalyst. In continuation of our research program involving the synthesis of fluorine containing reagents and their use for the synthesis of complex trifluoromethyl—containing organic systems of medicinal importance [29], [30],[31], [32], [33]. Therefore, we describe the first report of a facile synthesis of 9-(4-phenyl-substituted)-3.6-bis (trifluomethyl-3, 4, 5, 6, 7, 9-hexahydro-1H-xanthene-1, 8(2H)-dione by using this $ZrOCl_28H_2O$ catalyst.

2. MATERIAL AND METHODS

2.1. Experimental:

Melting points of the desired derivatives were determined using capillary melting apparatus, MELT-TEMP and were uncorrected. 1H NMR and 13C NMR

nuclear magnetic resonance spectra were taken on Bruker ARX 400 NMR instrument with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals were expressed as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiple). Coupling constant are in hertz (HZ). Mass spectra of these derivatives were recorded on Varian Saturn 2000 GC/MS. Each of the reaction was monitored and judged complete by removing aliquots at intervals and analysed by thin layer chromatography (TLC).

2.2.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS:

Take a dry and clean 25ml four necked RBF and fitted with on magnetic stirrer. A 20 ml fleshed ethanol poured into RBF and a mixture of 5-trifluoromethyl-1,3-cyclohexanedione 1 (2.2 mmol), and appropriate substituted aryl aldehyde 2 (1.5 mmol) added in RBF The organic acid catalyst a 5%mmol of $ZrOCl_2 8H_2O$ was added into the reaction. The reaction was continuing for two hours. The progress of the reaction was checked with help of TLC (EtOAc: n-Hexane-4:6) and after which the reaction mixture was cooled to room temperature (25˚C) to afford ethanol insoluble solid products. The products were recrystallized from ethanol to afford highly pure products.

Characterization of the derivatives:

2.2.1).9-phenyl-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)- Dione (3a):

White compound; Yield- 85%; MP: 202˚C - 204˚C. 1H NMR (400 MHz, CDCl3) δppm: 2.335 - 2.648 (m, 8H, cyclohexyl-Hs), 2.781 (m, 4H,-CH2-), 2.899 (m, 2H, CH to CF3), 4.482(s,1H,CH),7.264-7.438(m,5H,Ar-H);13CNMR(400MHz,CDCl3)δppm:193.46,192.95, 158.76,157.15,142.46,137.65,137.14,128.47,127.84,126.76,114.76,114.17,37.62, 1.64, 31.05, 27.42, 42.15, 20.92, 20.13.LCMS (m/z); 429.28(M-H): Molecularformule: $_{21}$H16F6O3: Elemental analysis: C-58.60; H- 3.74. Found: C- 58.55; H- 3.72.

2.2.2.9-(4-hydroxy-3-methoxyphenyl)-3,6-bis (trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(4b):

White compound, Yield-92%; MP: 256˚C - 258˚C. 1H NMR (400 MHz,CDCl3) δ ppm: 2.335 - 2.591 (m, 8H,cyclohexyl-Hs), 2.781 (m, 4H,-CH2-), 2.899 (m, 2H, CH to CF3), 4.482 (s, 1H, CH), 7.324 -7.434 (m, 5H, Ar-H), 8.897 (s, 1H, OH-Ar); 13C NMR (400 MHz, CDCl3) δppm:193.21, 193.09, 162.52, 162.11, 147.17, 145.08, 134.82, 128.65, 125.89, 121.09, 116.71, 115.60, 113.74, 56.88, 40.80, 40.40, 39.20, 36.85, 31.75, 25.88, 25.95; LCMS (m/z):475.22(M-H) ;Molecular Formulae: C22H18F6O5;Elemental Analysis: calculated: C-55.47; H-3.81: Obtained: C-55.40; H-3.79.

2.2.3.9-(p-tolyl)-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene1,8(2H)-dione (4c):

White compound .Yield-85%; MP: 191˚C - 193˚C. 1H NMR (400 MHz, CDCl3) δppm: 2.435 - 2.679 (m, 8H, cyclohexyl-Hs), 2.781 (m, 4H), 2.897 (m, 2H, CH to CF3), 4.482 (s,1H, CH), 7.324 -7.534 (m, 4H, Ar-H), 2.589 (s, 1H, CH3-Ar); 13C NMR (400 MHz, CDCl3)δppm: 193.07, 192.66, 162.73, 161.75, 141.70, 140.59, 136.87, 129.81, 128.59, 116.61,115.79,40.86,40.71,40.18,36.94,35.57,31.44,25.98,21.50:LCMS(m/z):443.09: MolecularFormulae: $C_{22}H_{18}F_6O_3$: Elemental Analysis: calculated: C-59.47,H-4.08: Obtained: C-59.41,H-4.07.

2.2.4.9-(4-ethylphenyl)-3,6-bis(trifluoromethyl)-3,4, 5,6,7-hexahydro-1H-Xanthane-1,8(2H)-dione (4d):

Whitecompound;Yield-87%;MP:199-201^{0}C;1HNMR(400MHz,CDCl3):7.214-7.045(m,4H, Ar-H),2.145(s,1H,-CH-), 2.108(d,J=6.0Hz,2H,-CH2), 1.732(t,J=7.6Hz,4H), 1.584(t,J=7.6Hz, 4H), 1.345 (t,J =6.8Hz,4H),0.982(s,3H,-CH3); ^{13}CNMR (400MHz, CDCl3) δppm: 193.99,193.14, 158.36, 157.81,140.09, 138.96,137.19, 136.69,128.56,127.84, 114.61,114.02,37.14,30.84,30. 14,29.36,27.33, 26.84, 19.31,18.66.:LCMS(m/z):459.37(M+H);MolecularFormulae: $C_{23}H_{20}F_6O_3$:ElementalAnalysis: calculated: C- 60.26,H-4.40: Obtained: C-60.21,H-4.38.

2.2.5.9-(4-fluorophenyl)-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (4e):

Whitecompound;Yield-89%;Mp:177˚C-179˚C. 1HNMR (400MHz,CDCl3) δppm:2.325-2.810 (m,8H,cyclohexyl-Hs), 2.856(m,4H,-CH2-), 2.949 (m,2H,CHnextoCF3),4.348(s,1H,-CH-), 7.449-7.630 (m,4H,Ar-H); 13CNMR (400MHz,CDCl3) δppm:195.88,161.77,149.80,137.37, 135.07, 129.16, 127.09,114.22,41.58,30.84,27.36,17.87;LCMS(m/z): 440.07(M+2); Molecular formula: $C_{21}H_{15}F_7O_3$:

Elemental analysis: Calculated: C-54.50; H- 4.34; Found: C- 54.44; H- 4.32.

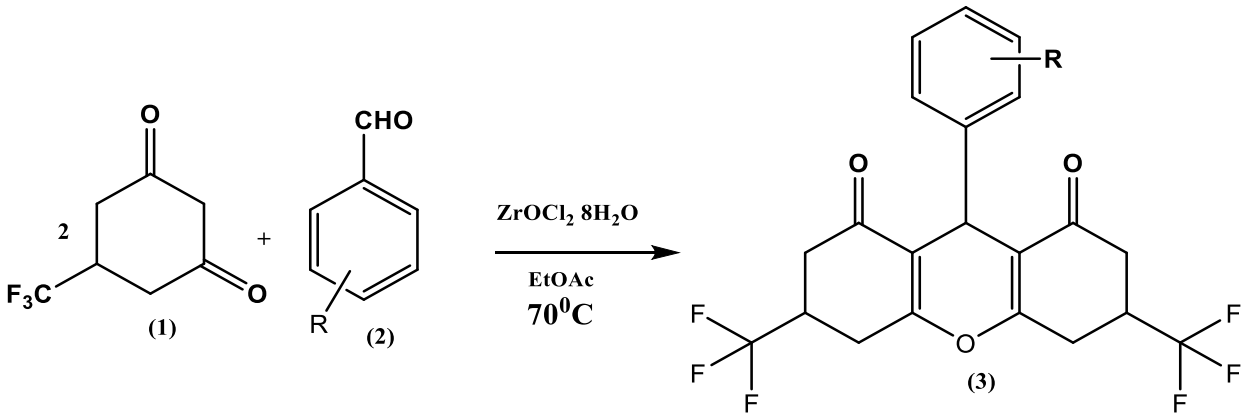
2.2.6.9-(4-chlorophenyl)-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(4f):
White compound; Yield-90%; MP: 181˚C-183˚C.1H NMR (400 MHz, CDCl3) δppm: 2.335- 2.679 (m, 8H, cyclohexyl-Hs),2.891(m,4H,-CH2-), 2.957 (m,2H,CH),4.372(s,1H,CH),7.349-7.660(m,4H,Ar-H;13CNMR(400MHz,CDCl3)δppm:195.55,161.27,141.22,137.33,130.14, 128.93, 128.02, 114.19, 38.87, 30.44,25.64,18.25.LCMS(m/z):466.36(M+2);Molecular Formulae: $C_{21}H_{15}ClF_6O_3$:Elemental Analysis; Caliculated:C- 58.61.; H- 3.75. Found: C- 58.58; H- 3.70.

2.2.7.9-(2,4-dichlorophenyl)-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (4g):
Yield-87%;MP:225˚C-227˚C.1HNMR(400MHz,CDCl3)δppm:2.335-2.571 (m,8H,cyclohexyl -Hs) , 2.781 (m, 4H), 2.899 (m, 2H, CH-to CF3), 4.482 (s,1H, CH), 7.324 -7.489 (dd, Ar-H), 8.475 (s,1H, 2Cl-Ar); 13C NMR (400 MHz,CDCl3) δppm: 192.98, 192.07, 1625.6, 161.79, 161.58, 140.82, 134.19, 133.42, 131.09, 128.98, 128.57,125.49, 114.76, 40.56, 40.41, 39.79, 36.81,35.28,30.72,25.98;LCMS(m/z):500.22(M+2); MolecularFormulae:C21H14Cl2F6O3; Elemental Analysis: calculated: C-50.53; H-2.82: Obtained: C-50.46; H-2.80:

2.2.8.4-(1,8-dioxo-3,6-bis(trifluoromethyl)-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl) benzonitrile(3h):
Yield-88%; MP: 205˚C- 207˚C. (1HNMR 400MHz,CDCl3) δppm: 2.324 - 2.802 (m, 8H, cyclohexyl-Hs), 2.784 (m, 4H), 2.557 (m, 2H, CH), 4.782 (s, 1H, CH), 7.489-7.610 (m, J = 8.0Hz,4H,Ar-H);13CNMR(400MHz,CDCl3)δppm:195.15,194.915, 162.46,162.57,145.77, 137.68,135.24,131.14, 128.96, 118.56,115.96,114.06,111.35,41.16,31.54,30.88,27.29,26.65,18.97,18.28.LCMS(m/z):455.36(M^+):MolecularFormulae:C22H15F6NO3:ElementalAnalysis: Calculated: C-58.03;H-3.30; N- 3.85: Obtained: C-57.92; H- 3.22; N- 3.90.

3. RESULTS AND DISCUSSION

The catalytic activity of $ZrOCl_28H_2O$ was first investigated using Two component reaction of substituted benzaldehyde, 5-trifluoromethyl-1,3-cyclohexanedione as a model reaction. After carrying out the reaction at various conditions, the best results have been obtained with 2.0 mol% $ZrOCl_28H_2O$ at RT. after 5 hrs with 85% yield under ethanol as solvent conditions. Our initial work started with screening of solvent and catalyst loading so as to identify optimal reaction conditions for the synthesis of 1, 8-Dioxo-Octahydroxanthene derivative. The solvents acetone, acetonitrile, ethanol, toluene and methanol were evaluated during the reaction condition reaction with no solvent at 70ºC was found to be the most successful. We also determined the amount of $ZrOCl_28H_2O$ required for the reaction, and it is concluded that 2.0 mol% of catalyst is sufficient to promote the reaction. Initially, conducted the reaction proceeded by conventional heating in ethanol containing $ZrOCl_28H_2O$ as a catalyst. The reaction was judged unsatisfactory after three trials, because of low yields, reaction time (4 - 5 h), and the need for purification by column chromatography. The corresponding conventional process of reaction was facile and gave well to excellent yields (85% - 95 %,) in 5hrs. The purity of each product was confirmed by sharp melting point and characterization by spectroscopic methods (IR, NMR, and LCMS). Under conventional heating process of reaction as shown in Scheme-1 and the reaction was completed giving low yield of product. All products showed strong absorption in the IR spectrum near 1665 cm−1 that is characteristic of a ketone carbonyl in conjugation with a double bond. The molecular ion corresponding to the molar mass of each product was observed as the largest m/z peak in each spectrum. The NMR data are consistent with the structure of the expected structure. The tricyclic component displayed a typical chemical shift of 4.82 ppm corresponding to the lone proton on the 9-position of the pyran core.



(3a=3h)

R = H , 4=OH, 3-OCH_3, 4-CH3 , 4-C_2H_5 , 4-F, 4-Cl, 2.6-$(Cl)_2$, 4-CN

(Scheme-1)

In order to evaluate the generality of this methodology, a range of desired product were synthesized under the optimized reaction conditions. The reaction condition of these derivatives was optimized at various catalyst, different amount of the catalyst and different solvent are used. The maximum yield of the compounds obtained in presence of $ZrOCl_2$ catalyst than oxidative related catalyst such as TiO_2, $FeCl_3$, $ZnCl_2$ whereas different amount of catalyst utilized during the reaction (Table-I).

Table-I: The effect of reaction of aryl aldehyde 5-trifluoromethyl cyclohexane-1, 3-dione

Entry	Catalyst	Catalyst amount(mmol)	Time (h)	Yield (%)
1	TiO_2	2.0	08	55
2	$FeCl_3$	2.0	07	76
3	$ZnCl_2$	2.0	10	49
4	$ZrOCl_2$	2.0	05	95

4. CONCLUSION

A highly efficient introduction of a trifluoromethyl group into biologically active xanthenedione is achieved. In conclusion, we have developed an efficient one pot multicomponent synthesis of 9-phenyl-3,6-bis(trifluoromethyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione derivatives using $ZrOCl_2 8H_2O$ as the catalyst. The different substituted aldehyde was efficiently converted in combination with 5-trifluoromethyl cyclohexane-1, 3-dione in excellent yields. Furthermore, the simple experimental procedures, utilization of an inexpensive and readily available eco-friendly catalyst are the advantages of present methodology. This protocol proceeds with high atom-efficiency and shows a broad substrate scope and functional group tolerance, making it a highly practical approach for preparation of pharmaceutically interesting various substituted aldehydes.

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REFERENCE

[1] Lipson, V.V., Desenko, S.M., Shirobokova, M.G. and Borodina, V.V. (2003) Synthesis of9-Aryl-6,6-Dimethyl-5,6,7,9-Tetrahydro-1,2,4-Triazolo-[5,1-

B]quinazolin-8(4H)Ones. ChemistryofHeterocyclicCompounds,39,1419-1427.

[2] Robinson, R. (1958) Chemistry of Brazilin and Haematoxylin. Bulletin de la Société chimique de France, 1, 125-134.

[3] Yen, C.-T., Nakagawa-Goto, K., Hwang, T.-L., Wu, P.-C., Morris-Natschke, S.L., Lai, W.-C., Bastow, K.F., Chang, F.-R., Wu, Y.-C. and Lee, K.-H. (2010) Antitumor Agents. 271: Total Synthesis and Evaluation of Brazilin and Analogs as Anti-Inflammatory and Cytotoxic Agents. Bioorganic & Medicinal Chemistry Letters, 20, 1037-1039.

[4] Huang, Y., Zhang, J. and Pettus, T.R.R. (2005) Synthesis of (±)-Brazilin Using IBX. Organic Letters, 7, 5841-5844.

[5] Manikannan, R., Venkatesan, R., Muthusubramanian, S., Yogeeswari, P. and Sriram, D. (2010) Pyrazole Derivatives from Azines of Substituted Phenacyl Aryl/Cyclohexyl Sulfides and Their Antimycobacterial Activity. Bioorganic & MedicinalChemistryLetters,20,6920-6924.

[6] Bhaskara, N., Ankita, C., Anshika, L. and Jitender, M.K. (2015) Synthesis and Characterization of Hybrid Chloroquinoline-Xanthene Derivatives. Cogent Chemistry,1, Article ID: 1071227.

[7] Giri, R., Goodell, J.R., Xing, C., Benoit, A., Kaur, H., Hiasa, H. and Ferguson, D.M. (2010) Synthesis and Cancer Cell Cytotoxicity of Substituted Xanthenes. Bioorganic & Medicinal Chemistry, 18, 1456-1463.

[8] Parkin, D.M., Bray, F., Ferlay, J. and Pisani, P. (2002) Global Cancer Statistics. CA:A Cancer Journal for Clinicians, 55, 74-108.

[9] Faidallah, H.M., Khan, K.A. and Asiri, A.M. (2011) Synthesis and Biological Evaluation of New 3,5-di(trifluoromethyl)-1,2,4-triazolesulfonylurea and Thiourea Derivatives as Antidiabetic and Antimicrobial Agents. Journal of Fluorine Chemistry,132, 870-877.

[10] Aytemir, M.D., Hider, R.C., Erol, D.D., et al. (2003) Synthesis of New Antimicrobial Agents; Amide Derivatives of Pyranones and Pyridinones. Turkish Journal of Chemistry, 27, 445-452.

[11] Yildirir, Y., Us, M.F., Colak, N., Özkan, H., Yavuz, S., Dişli, A., Öztürk, Ş. andTürker, L. (2009) The Synthesis and Investigation of the Antimicrobial Activity of Some New Phenylselanyl-1-(toluene-4sulfonyl)-1Htetrazole Derivatives. Medicinal Chemistry Research, 18, 91-97.

[12] Alyar, S. and Karacan, N. (2009) Synthesis, Characterization, Antimicrobial Activity and Structure-Activity Relationships of New Aryldisulfonamides. Journal of Enzyme InhibitionandMedicinal Chemistry, 24, 986-992.

[13] Wang, H., Lu, L., Zhu, S., Li, Y. and Cai, W. (2006) The Phototoxicity of Xanthene Derivatives against Escherichia coli, Staphylococcus aureus, and Saccharomyces cerevisiae. Current Microbiology, 52, 1-5.

[14] Qiao, Y.F., Okazaki, T., Ando, S., Mizoue, K., Kondo, K., Eguchi, T., et al. (1998) Isolation and Characterization of a New Pyrano[4',3':6,7]naphtho [1,2-b]xanthene Antibiotic FD-594. The Journal of Antibiotics, 51, 282-287.https://doi.org/10.7164/antibiotics.51.282

[15] Limsuwan, S., Tripc, E.N., Kouwen, T.R.H.M., Piersma, S., Hiranrat, A., Mahabusarakam, W., et al. (2009) Rhodomyrtone: A New Candidate as Natural Antibacterial Drug from Rhodomyrtus tomentosa. Phytomedicine, 16, 645-651