Synthesis of New 1, 8-Dioxo-Octahydroxanthene Derivatives Containing 4-Thiazolidinone Moiety

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ABSTRACT: *A series of novel 1, 8-dioxo-octahydroxanthene derivatives containing 4-thiazolidinone framework (4a-f) were synthesized through a four-step reaction starting from the reduction of nitro derivatives of 1, 8-dioxo-octahydroxanthenes. The resulting aminoxanthenes converted to thiourea derivatives via their reaction with methyl isothiocyanate. The final products were synthesized through the reaction of thiourea derivatives with dialkylacetylene dicarboxylates. All of the steps were carried out under easy and mild reaction conditions in the absence of expensive catalysts or esoteric starting materials. The structures of compounds 3a-c and the final products were characterized according to their physical constants, spectral data such as NMR, IR spectra and also elemental analysis.*

KEYWORDS: *1, 8-dioxo-octahydroxanthene; 4-thiazolidinone; Dialkyl acetylenedicarboxylate; Dimedone; 1, 3-cyclohexanedione.*

INTRODUCTION

There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulfur, and oxygen, which have always drawn the attention of chemist over the years.

In particular, two types of heterocyclic compounds are attracting a lot of attention, xanthene, and thiozolidinone.

Xanthene derivatives have received significant attention in the past due to their wide range of biological properties [1-3].One of the main applications of xanthene derivatives is their usage as dyes[4], pH-sensitive fluorescent materials for visualization of biomolecules[5] and in laser technologies[6].

Another heterocyclic nucleus that has been subjected to extensive studies is thiazolidinone. The 4- thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs.They have been found uses such as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agents. Numerous reports have appeared in the literature which highlight their chemistry and pharmacological uses [7-10]. One of the most important methods for synthesis of organic compounds is MultiComponent Reactions (MCRs). Multi-component reactions are useful tools for the preparation of innovative

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and very complex scaffolds according to a convergent approach, providing a molecule that contains fragments derived from all the building blocks [11-17].

In continuation of our work on the synthesis of heterocyclic compounds [18-21] herein, we wish to report a convenient and efficient method for the preparation of 1, 8-dioxo-octahydroxanthenederivatives containing a 4-thiazolidinone moiety (**4a-f**).

EXPERIMENTAL SECTION

Dimethyl acetylenedicarboxylate (DMAD), dialkyl acetylenedicarboxylate (DAAD), dimedone, 1, 3-cyclohexanedione, 3-nitro & 4-nitro benzaldehyde, $SnCl_2.2H_2O$ methyl isothiocyanate and all of the solvents were purchased from Merck Chemical Company and were used without further purification.

Compounds **1a-c** and **2a-c** are known and synthesized according to the literature [22-23]and identified by comparison of their spectral data and physical properties with those of the authentic samples. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER Ultrashield-400 NMR spectrometer using DMSO as a solvent. IR spectra were recorded on a BRUKER Tensor-27 FT-IR spectrophotometer using KBr pellets. Melting points were obtained in open capillary tubes and were measured on an Electrothermal-9100 apparatus. Elemental analyses data were obtained using LECO-932 series apparatus.

Synthesis of 1-(1, 8-dioxo-1H-xanthen-9-yl)phenyl-3-methylthiourea derivatives 3a-c:

A mixture of amino xanthene **2** (1 mmol) and methyl isothiocyanate (1 mmol) in 10 mL of ethanol was refluxed for 3h and then the reaction mixture poured into cold water and resulted precipitate was recrystallized from ethanol to afford the pure title products as white solids.

*1-(4-(2, 3, 4, 5, 6, 7, 8, 9-octahydro-3, 3, 6, 6-tetramethyl-1, 8-dioxo-1H-xanthen-9-yl)phenyl)-3-methylthiourea (**3a**)*

IR (KBr): υ_{max} = 1667, 2870, 2957, 3312 cm^{-1};^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 0.93 (6H, s, $2CH_3$), 1.03 (6H, s, $2CH_3$), 2.05-2.18 (4H, m, $2CH_2$), 2.42 (4H, m, $2CH_2$), 2.97 (3H, s, N- CH_3), 4.58 (1H, s, CH), 6.96 (1H, s, brd- NH), 7.12-7.14 (2H, m, arom), 7.59-7.60 (2H, m, arom), 8.94 (1H, s, brd- NH); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 26.9, 28.5, 30.7, 31.0, 31.7, 40.1, 50.2, 114.5, 122.8, 128.6, 136.0, 128.6, 136.0, 140.7, 162.2, 180.8 (C=S), 195.8 (C=O).Anal. Calcd. For $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.39%. Found. C, 68.18; H 6.75; N6.12%.

*1-(3-(2, 3, 4, 5, 6, 7, 8, 9-octahydro-3, 3, 6, 6-tetramethyl-1, 8-dioxo-1H-xanthen-9-yl) phenyl)-3-methylthiourea (**3b**)*

IR (KBr): υ_{max} = 1666, 2870, 2957, 3315, 3369 cm^{-1};^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 0.93 (6H, s, $2CH_3$), 1.03 (6H, s, $2CH_3$), 2.05-2.18 (4H, m, $2CH_2$), 2.39-2.42 (4H, m, $2CH_2$), 2.89 (3H, s, N-CH_3), 4.56 (1H, s, CH), 6.87 (1H, s, brd, NH), 6.90-6.95 (1H, m, arom), 7.04-7.12 (1H, m, arom), 7.23 (1H, s, arom), 7.46-7.50 (1H, m, arom), 8.88 (1H, s, brd, NH);^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 26.9, 28.5, 31.1, 31.5, 31.6, 40.1, 50.2, 114.3, 121.2, 124.0, 124.4, 128.5, 136.8, 144.9, 162.2, 180.7 (C=S), 196.0 (C=O). Anal. Calcd. For $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.39%. Found. C, 68.22; H, 6.72; N, 6.19%.

*1-(3-(2, 3, 4, 5, 6, 7, 8, 9-octahydro-1, 8-dioxo-1H-xanthen-9-yl) phenyl)-3-methylthiourea (**3c**)*

IR (KBr): υ_{max} = 1673, 2888, 2945, 3028, 3175, 3381 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 1.89-1.99 (4H, m), 2.27- 2.30 (4H, m), 2.59-2.68 (4H, m), 2.93 (3H, s, N-CH_3), 4.59 (1H, s, CH), 6.97 (1H, d, J= 7.6 Hz, arom), 7.12 (1H, t, J= 8 Hz, arom), 7.21- 7.23 (2H, m, arom), 8.23 (2H, s, brd, 2NH); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 28.5, 31.1, 31.5, 31.6, 40.1, 50.2, 114.3, 121.2, 124.0, 124.4, 128.5, 136.8, 144.9, 162.2, 180.7 (C= S), 196.0 (C= O). Anal. Calcd. For $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32%. Found. C, 65.67; H, 5.73; N, 6.98%.

Synthesis of thiazolidinone derivatives (4a-f):

To a magnetically well-stirred solution of thiourea derivatives, **3** (1 mmol) in ethanol (10mL) dimethyl acetylenedicarboxylate (DMAD) (1.2 mmol) was added at the ambient temperature. The reaction mixture was then stirred for the appropriate time (monitored by TLC) at room temperature. The solvent was removed under reduced pressure and the residue recrystallized from 2:1 hexane-chloroform affording the desired products as pale yellow crystals.

*Methyl (Z)-2-((E)-3-methyl-4-oxo-2-((4-(3, 3, 6, 6-tetramethyl-1, 8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino)thiazolidin-5-ylidene)acetate **(4a)***

IR (KBr): υ_{max} = 1668, 1704, 1727, 2871, 2957 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 0.95 (6H, s, $2CH_3$), 1.06 (6H, s, $2CH_3$), 2.12- 2.58 (4H, m, $2CH_2$), 2.51 (4H, m, $2CH_2$), 3.29 (3H, s, N-CH_3), 3.73 (3H, s, O-CH_3), 4.58 (1H, s, CH), 6.77 (1H, s, CH-Vinyl), 6.82 (2H, d, J= 8.4 Hz, arom), 7.21 (2H, d, J= 8.4 Hz, arom); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 26.7, 28.6, 29.0, 30.7, 31.8, 39.9, 50.1, 52.2 (OCH_3), 114.4, 115.0, 120.3, 128.8, 140.9, 141.2, 144.9, 150.4, 162.5, 164.0, 165.5, 195.6 (C= O); Anal. Calcd. For $C_{30}H_{32}N_2O_6S$: C, 65.67; H, 5.88; N, 5.11%. Found. C, 65.44; H, 5.67; N, 5.33%.

*Ethyl (Z)-2-((E)-3-methyl-4-oxo-2-((4-(3, 3, 6, 6-tetramethyl-1, 8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino)thiazolidin-5-ylidene)acetate **(4b)***

IR (KBr): υ_{max} = 1669, 1697, 1724, 2871, 2959 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 0.95 (6H, s, $2CH_3$), 1.08 (6H, s, $2CH_3$), 1.23 (3H, t, J= 7.2 Hz, CH_3), 2.11-2.23 (4H, m, $2CH_2$), 2.49 (4H, m, $2CH_2$), 3.29 (3H, s, N-CH_3), 4.17 (2H, q, J= 7.2 Hz , CH_2), 4.58 (1H, s, CH), 6.74 (1H, s, CH-Vinyl), 6.80 (2H, dd, J_1= 8.4 Hz, J_2= 2.4 Hz, arom), 7.20 (2H, dd, J_1= 8.4 Hz, J_2= 2.4 Hz, arom); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 13.7, 26.7, 28.6, 29.0, 30.7, 31.7, 40.2, 50.1, 61.1, 114.4, 115.4, 120.2, 128.8, 140.9, 144.8, 150.4, 162.4, 164.0, 165.0, 195.6 (C= O);Anal. Calcd. For $C_{31}H_{34}N_2O_6S$: C, 66.17; H, 6.09; N, 4.98%. Found. C, 65.95; H, 6.17; N, 4.64%.

*Methyl (Z)-2-((E)-3-methyl-4-oxo-2-((3-(3, 3, 6, 6-tetramethyl-1, 8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino)thiazolidin-5-ylidene)acetate **(4c)***

IR (KBr): υ_{max} = 1666, 1726, 2871, 2957 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 0.77 (6H, s, $2CH_3$), 0.86 (6H, s, $2CH_3$), 1.99 (4H, m, $2CH_2$), 2.27-2.32 (4H, m, $2CH_2$), 3.14 (3H, s, N-CH_3), 3.55 (3H, s, O-CH_3), 4.4 (1H, s, CH), 6.51 (1H, s, CH-vinyl), 6.58 (2H, d, J_1= 9.2 Hz), 6.90 (1H, s, arom), 6.99 (1H, s, arom);^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 27.0, 28.3, 29.0, 31.2, 31.7, 40.0, 50.2, 52.0 (OCH_3), 114.3, 115.1, 119.0, 120.0, 125.1, 128.3, 141.2, 145.3, 146.7, 150.7, 162.3, 164.0, 165.4, 195.6 (C= O).Anal. Calcd. For $C_{30}H_{32}N_2O_6S$: C, 65.67; H, 5.88; N, 5.11%. Found. C, 65.50; H, 5.62; N, 4.87%.

*Ethyl (Z)-2-((E)-3-methyl-4-oxo-2-((3-(3, 3, 6, 6-tetramethyl-1, 8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino)thiazolidin-5-ylidene)acetate **(4d)***

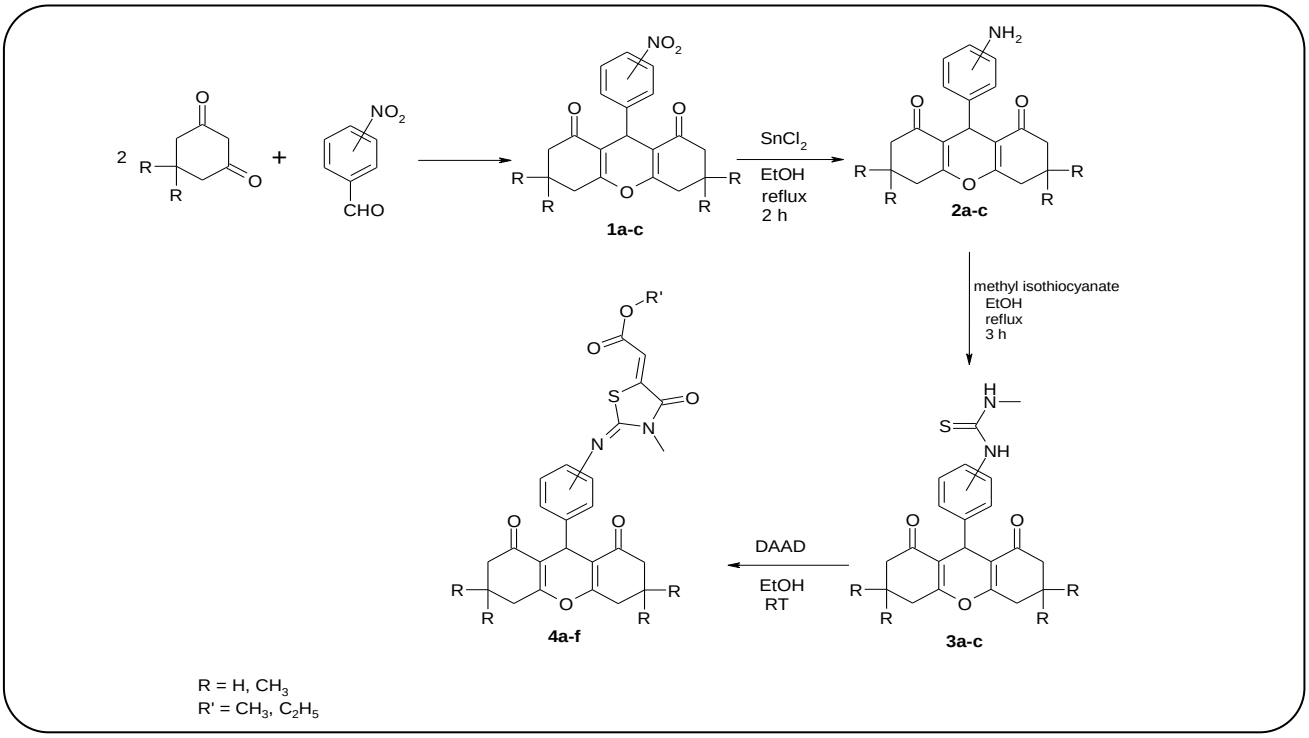
IR (KBr): υ_{max} = 1668, 1697, 1724, 2871, 2959 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 0.93 (6H, s, $2CH_3$), 1.03 (6H, s, $2CH_3$), 1.22 (3H, t, , J= 7.2 Hz, CH_3), 2.13-2.28 (4H, m, $2CH_2$), 2.54 (4H, m, 2 CH_2), 3.29 (3H, s, N- CH_3), 4.17-4.22 (2H, q, J= 7.2 Hz, CH_2), 4.58 (1H, s, CH), 6.74 (1H, s, CH-vinyl), 6.76 (1H, s, arom), 6.80 (1H, m, arom), 7.05 (1H, d, J= 8 Hz, arom), 7.25 (1H, t, J= 8 Hz, arom);^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 13.9, 26.7, 28.3, 29.2, 31.1, 31.8, 39.7, 50.0, 61.3, 114.1, 115.1, 119.0, 120.3, 124.8, 128.7, 141.3, 145.5, 146.9, 151.2, 162.9, 164.2, 165.1, 195.9;Anal. Calcd. For $C_{31}H_{34}N_2O_6S$: C, 66.17; H, 6.09; N, 4.98%. Found. C, 66.43; H, 6.22; N, 5.24%.

*Methyl (Z)-2-((E)-2-((3-(1, 8 -dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino) -3-methyl-4-oxothiazolidin-5-ylidene)acetate **(4e)***

IR (KBr): υ_{max} = 1654, 1702, 1728, 2893, 2948 cm^{-1};^1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.96 (4H, m), 2.28- 2.32 (4H, m), 2.56- 2.68 (4H, m), 3.32 (3H, s, N-CH_3), 3.74 (3H, s, O-CH_3), 4.63 (1H, s, CH), 6.74 (1H, d, J= 7.6 Hz, arom), 6.77 (2H, s, arom& CH-vinyl), 7.11 (1H, d, J= 7.6 Hz), 7.208 (1H, t, J= 7.6 Hz, arom);^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 19.8, 26.5, 29.1, 30.9, 36.3, 52.1, 115.0, 115.4, 119.2, 120.0, 125.3, 128.5, 141.3, 145.7, 146.7, 150.9, 164.1, 164.3, 165.5, 195.8; Anal. Calcd. For $C_{26}H_{24}N_2O_6S$: C, 63.40; H, 4.91; N, 5.69%. Found. C, 63.19; H, 4.76; N, 5.52%.

*Ethyl (Z)-2-((E)-2-((3-(1, 8 -dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthen-9-yl)phenyl)imino)-3-methyl-4-oxothiazolidin-5-ylidene)acetate **(4f)***

IR (KBr): υ_{max} = 1654, 1691, 1727, 2899, 2944, 3061 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 1.24 (3H, t, J= 7.2 Hz, CH_3), 1.95-1.97 (4H, m), 2.23- 2.32 (4H, m), 2.51-2.66 (4H, m), 3.33 (3H, s, N-CH_3), 4.17 (2H, q,



Scheme 1. Four-step synthesis of 1, 8-dioxo-octahydroxanthenes derivatives containing a 4-thiazolidinone.

J= 7.2 Hz, CH_2), 4.65 (1H, s, CH), 6.69- 6.73 (2H, m, arom), 6.76 (1H, s, CH-vinyl), 7.11-7.18 (2H, m, arom); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 13.73, 19.7, 26.5, 29.0, 30.9, 36.3, 61.0, 115.5, 115.6, 119.2, 119.8, 125.3, 128.3, 140.9, 145.5, 146.6, 150.8, 164.0, 164.1, 165.1, 195.9; Anal. Calcd. For $C_{27}H_{26}N_2O_6S$: C, 64.02; H, 5.17; N, 5.53%. Found. C, 63.71; H, 4.98; N, 5.18%.

RESULTS AND DISCUSSION

In order to prepare 1, 8-dioxo-octahydroxanthene derivatives containing 4-thiazolidinone a four-step synthesis is outlined in Scheme 1.

The first step of this synthetic route is the preparation of various nitro 1, 8-dioxo-octahydroxanthene derivatives **1** from the reaction of dimedone or 1,3-cyclohexanedione with various nitro benzaldehydes.

The second step is the synthesis of the amino octahydroxanthene derivatives **2**. There are various procedures for the reduction of nitroaromatic compounds to aniline derivatives.

Examination of some of these procedures gave unsatisfactory results. It seems that those methods did not work as efficiently as we expected for the selected reaction. We observed that $SnCl_2.2H_2O$ in alcohol work very efficiently [24] and led to the formation of compounds **2** in good yields.

In the third step, the compounds **3** were obtained easily by heating the mixture of amino derivatives **2** and methyl isothiocyanate in ethanol.

In the fourth step, final products **4** were obtained easily by the reaction of thiourea derivatives **3** in the presence of dialkyl acetylene dicarboxylate (DAAD) in ethanol as a solvent at ambient temperature. The results are summarized in Table 1.

The structures of all of the products were confirmed on the basis of their spectroscopic detailed in the Experimental section.

For example compound, **3b** revealed two bands in the IR spectrum for NH bond at 3369 and 3315 cm^{-1}. The ^{1}H NMR spectrum of **3b** revealed a singlet at 4.56 ppm for CH proton of xanthene ring and two singlets at 7.50 and 8.80ppm for two NH protons.

The ^{1}H NMR spectrum of **4c** shows two distinct peaks at 3.14 and 3.55 ppm, which are due to the methyl protons of N-CH_3 and OCH_3, along with a signal for vinylic CH proton at 6.51. In the corresponding ^{1}H-NMR spectrum, the disappearance of NH protons confirmed the formation of thiazolidinone ring. The ^{13}C NMR of

Table 1: Synthesis of compounds 3a-c and 4a-f.

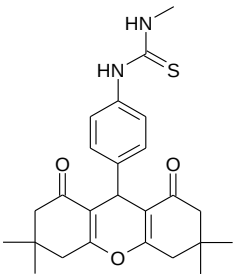
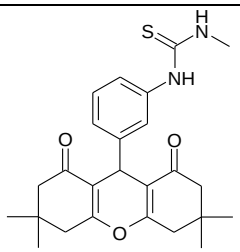
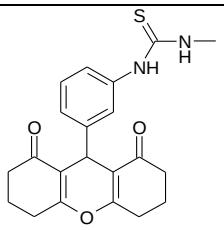
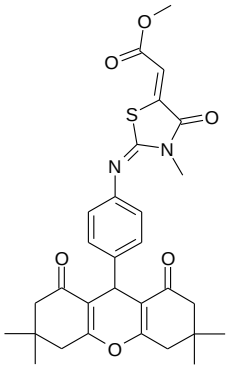
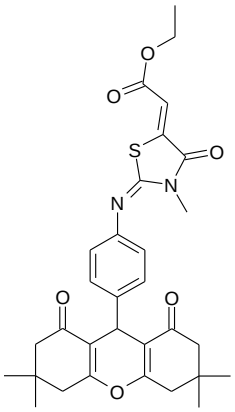
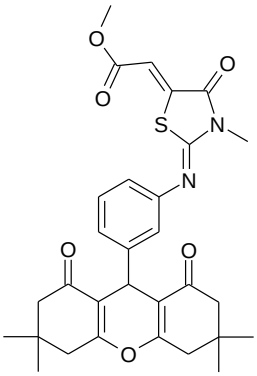
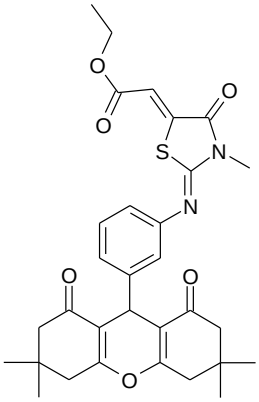
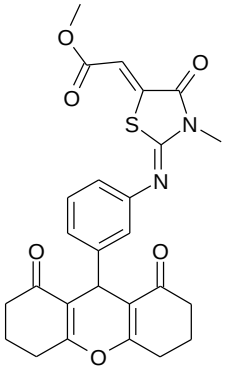
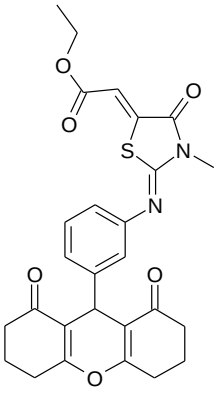
entry	structure	Time (min)	Yield%	Mp (ºC)
3a		180	80	145-148
3b		180	80	134-137
3c		180	75	245-248
4a		120	90	210-212
4b		150	85	190-193

Table 1: Synthesis of compounds 3a-c and 4a-f. (cont.)

4c		120	88	205-208
4d		150	80	150-153
4e		120	85	200-202
4f		150	80	222-225

compound **4c** is in good agreement with the proposed structure of this compound.

CONCLUSIONS

In summary new thiazolidin-4-one derivatives were synthesized under simple reaction conditions. In addition, nontoxic solvents were used and no special apparatus is needed to perform such a reaction. The present methodology is a versatile synthetic approach for the synthesis of xanthene derivatives containing thiazolidinone rings.

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