International Journal of Advanced Research in Chemical Science (IJARCS)
Volume 2, Issue 10, October 2015, PP 1- 6
ISSN 2349-039X (Print) & ISSN 2349-0403 (Online)
www.arcjournals.org

One Pot Facile Synthesis of some New γ, γ- Disubstituted Butenolides

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Abstract: *Synthesis of a novel series of γ, γ- disbstituted butenolides with a thiophene moiety is described. The synthetic target is achieved by a simple protocol involving condensation of β-(2-thenoyl) acrylic acid and β-(5-chloro-2-thenoyl)acrylic acid with different mono, di and trihydroxy phenols. The synthesized compounds were characterized by microanalysis and spectroscopic studies.*

Keywords: *Butenolides, β-(2-thenoyl)acrylic acid, β-(5-chloro-2-thenoyl)acrylic acids, phenols.*

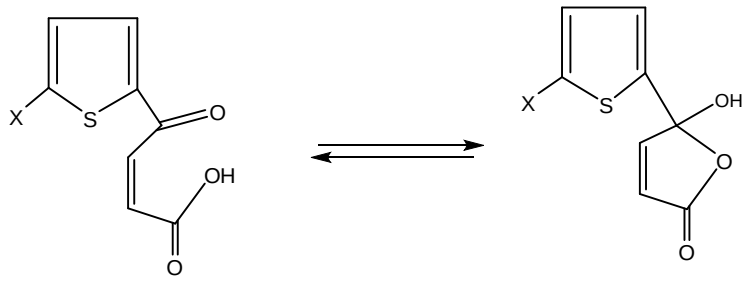
1. INTRODUCTION

Butenolides are five membered α, β-unsaturated cyclic esters and constitute central part in the structures of vast number of naturally occurring compounds [1-9]. They possess a characteristic γ-lactonic structure with four carbon and one oxygen heterocyclic ring system. Butenolides are also regarded as oxidized derivatives of furan and consequently, often referred as furanones. Butenolides are well known for their medicinal properties such as antitumour, antifungal and antibacterial activities [10]. Large number of synthetic drug candidates with diverse biological properties are associated with butenolide structure [11-17]. Chemistry of butenolides has received further attention due to the fact that they are attractive building blocks in the synthesis of some useful natural products [4, 18] and are present in large number of important compounds, e.g., alkaloids [19], lignans [20], insect pheromones [21], cardenolides [22] and flavour components [23] etc. as their structural moieties. Thus, continuously a great deal of attention is being devoted towards the development of new strategies and methodologies for the synthesis of such versatile scaffolds.

Taking into consideration the wide ranging biological properties and synthetic potential associated with the butenolides, we thought it worthwhile to synthesize a novel series of α, β- unsaturated- γ-butenolides having thiophene moiety in their structure which are expected to have antimicrobial properties. The devastating situation caused by speread of the antibiotic resistant strains of bacteria is causing a serious problem to human health all over the globe. Therefore, there is necessity of new and more effective antimicrobial agents. In the present work we have designed the synthesis of α, β-unsaturated- γ-butenolides (**4-9**) in which their γ-carbon atom is attached to a hydroxyphenyl ring and a thiophene ring. Among the various heterocyclic compounds that have been explored for the development of medicinally useful compounds, thiophene and its derivatives are of enormous interest. Thiophenes have been reported to possess remarkable antibacterial, antifungal, antiviral, nematocidal and insecticidal properties [24]. Due to their photodynamic character, thiophenes are of agricultural and medicinal interest as potential therapeutic agents and biorational pesticides [25]. Thiophene moiety is present in many pharmacologically active compounds, such as pyrantel, ticlopidine and cyclooxygenase-2 inhibitors [26].

2. RESULTS AND DISCUSSION

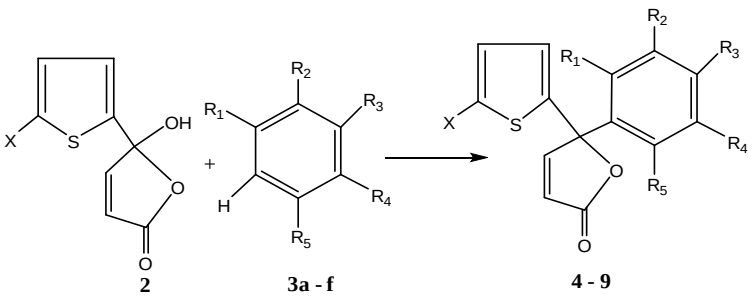
In the present work a number of new butenolides **4-9** have been synthesized by the reaction of two γ-keto acids, β-(2-thenoyl)acrylic acid **1a** and β-(5-chloro-2-thenoyl)acrylic acid **1b** with various mono-, di-, and trihydroxy phenols (**3a-3f**) in presence of catalytic amount of concentrated sulphuric acid. The method is simple and environmentally benign as it does not require any solvent. The occurrence of keto-lactol tautomerism in γ–keto and γ–formyl acids is well documented [27]. In many chemical reactions these acids participate through cyclic lactol form [28]. The keto-acid (**1**) and lactol (**2**) tautomeric forms of β-(2-thenoyl)acrylic acid and β-(5-chloro-2-thenoyl)acrylic acid may be depicted as shown in Scheme 1. These two acids (**1**) reacted with phenols (**3a-f**) through their lactol form (**2**) as shown in Scheme 2.



1a : X = H
1b : X = Cl

2a : X = H
2b : X = Cl

Scheme1. *Keto – acid and lactol taautomeric forms of β-(2-thenoyl)acrylic acid and β-(5-chloro-2-thenoyl)acrylic acids.*



2 **3a - f** **4 - 9**

3a, 4 : $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$ **3d,** 7 : $R_2 = R_3 = R_5 = H$; $R_1 = R_3 = OH$
3b, 5 : $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OH$ **3e,** 8 : $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = OH$
3c, 6 : $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = OH$ **3f,** 9 : $R_4 = R_5 = H$; $R_1 = R_2 = R_3 = OH$
2a, 4a - 9a : X = H; and **2b, 4b - 9b** : X = Cl

Scheme2. *Synthesis of γ,γ-disubstituted -$\Delta^{\alpha\beta}$–butenolides **4–9.***

In the structure of synthesized butenolides **4-9** the γ–carbon of the butenolide ring is attached to two different rings. One is a phenyl ring containing one, two or three hydroxy groups, and the other is a thienyl ring with or without a chlorine atom. The synthesized compounds may be regarded as γ,γ-disubstituted butenolides. Structure elucidation of these new compounds is based on elemental analysis, UV, IR and ^{1}H NMR spectral data.

The γ,γ- disubstituted butenolides **4-9b** in their IR spectra (in KBr, ν_{max} in cm^{-1}) exhibited two sharp and strong peaks near 1775–1785 cm^{-1} which are characteristic of five membered α, β–unsaturated γ–lactonic ring (ν CO). A prominent band noticed at 1615–1625 cm^{-1} supports the presence of an olephenic double bond (ν C=C) of butenolide ring. The hydroxyl groups in phenolic rings of all the butenolides gave a strong and broad IR absorption band near 3300–3424 cm^{-1}. UV spectra (in ethanol) showed the presence of bands at 250–260, 300–320 and 340–360 nm. In the ^{1}H NMR spectra (in DMSO-d_6) of the butenolides, α-olefinic proton gave a doublet at δ6.10-6.20, while the doublet of β-olephinic proton was shifted to downfield and appeared with protons of thienyl and phenyl rings as a complex multiplet in the region between δ6.35 and 8.15. Signals of hydroxy protons of phenolic rings were visible in the region between δ4.10 and 5.60.

3. EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer using KBr pellets. UV/Vis spectra were taken on Perkin-Elmer

Lambda 15 UV/Vis spectrophotometer. ^{1}H NMR spectra were obtained on a Varian FT-80A spectrophotometer using DMSO-d_6 as solvent. Chemical shifts are reported in δ (ppm). Using TMS as Standerd Progress of the reactions and homo genecity of the products were monitored by TLC β-(2-thenoyl)acrylic acid **1a** and β-(5-chloro-2-thenoyl)acrylic acid **2a** were senthesized by a literature procedure [29]. The phenols (phenol, resorcinol, catechol, quinol, phloroglucinol and pyrogallol) were taken in slight excess over the acid **1**.

4. General Procedure for the Synthesis of Butenolides 4–9

An intimate mixture of β-(2-thenoyl)acrylic acid **1a** or β-(5-chloro-2-thenoyl)acrylic acid **1b** (0.01 mol) and phenolic compound **3a-f** (0.015 mol) was heated in an oil bath to get a homogenous molten mass. To this, catalytic amount of concentrated sulphuric acid (3–4 drops) was added dropwise with stirring. The heating was continued for 1h to 4h (monitored by TLC) to obtain a hard and brittle solid mass on cooling. It was crushed and washed with cold water to remove the remaining unreacted phenolic compound. The process of steam distillation was employed to remove the unreacted phenol in the synthesis of **4a, b**. The crude condensed mass so obtained was dissolved in 2% aqueous sodium hydroxide and filtered. The filtrate was cooled in ice-cold water and acidified by adding dil.HCl gradually with stirring to afford the butenolides **4-9**. The crude butenolides were purified by column chromatography using silica gel as absorbant and benzene - ethanol (80:20) as eluent. The eluted compounds were crystallized with aqueous ethanol, dried in an oven at 100 ^{0}C and finally over phosphorous pent oxide in a vaccum desicator.

The conditions of the reactions, physical data and yields of the synthesized γ, γ- disubstituted butenolides are summarized in **Table 1**. The results of their spectroscopic investigations are given below.

Table1. *Preparation and physical data of γ, γ - disubstituted -$_{\Delta}^{\alpha\beta}$–butenolides **4a - 9a** and **4b - 9b***

Butenolide*	Reaction		M. p. (^{0}C)	Yield (%)	Mol. Formula	Analysis (%) Cacld (Found)			
	Temp (^{0}C)	Time (h)				C	H	S	Cl
4a	158 - 168	3.5	171 - 172	60	$C_{14}H_{10}O_3S$	65.12 (65.15)	3.80 (3.75)	12.40 (12.43)	- -
4b	160 - 170	4.0	175 - 177	62	$C_{14}H_9O_3SCl$	57.44 (57.56)	3.08 (3.10)	10.94 (10.89)	12.17 (12.21)
5a	135 - 145	2.5	140 - 142	65	$C_{14}H_{10}O_4S$	61.31 (61.33)	3.65 (3.70)	11.68 (11.71)	- -
5b	130 - 140	2.0	136 - 138	68	$C_{14}H_9O_4SCl$	54.46 (54.61)	2.92 (2.94)	10.37 (10.29)	11.50 (11.43)
6a	156 - 166	3.5	148 - 150	70	$C_{14}H_{10}O_4S$	61.31 (61.22)	3.65 (3.81)	11.68 (11.72)	- -
6b	160 - 170	3.0	155 - 157	72	$C_{14}H_9O_4SCl$	54.46 (54.60)	2.92 (2.95)	10.37 (10.40)	11.50 (11.43)
7a	190 - 200	4.0	153 - 155	65	$C_{14}H_{10}O_4S$	61.31 (60.92)	3.65 (3.70)	11.68 (11.80)	- -
7b	210 - 220	3.5	166 - 168	60	$C_{14}H_9O_4SCl$	54.46 (54.28)	2.92 (2.90)	10.37 (10.33)	11.50 (11.45)
8a	195 - 205	2.5	151 - 153	75	$C_{14}H_{10}O_5S$	57.93 (57.77)	3.45 (3.42)	11.03 (10.90)	- -
8b	200 - 210	2.0	145 - 147	65	$C_{14}H_9O_5Cl$	51.77 (51.50)	2.77 (2.75)	9.86 (9.91)	10.93 (10.81)
9a	185 - 195	1.5	>300 (Decomp)	62	$C_{14}H_{10}O_5S$	57.93 (57.87)	3.45 (3.50)	11.03 (11.12)	- -
9b	165 - 175	1.0	296 - 298	68	$C_{14}H_9O_5Cl$	51.77 (51.98)	2.77 (2.78)	9.86 (9.83)	10.93 (10.98)

**Brown microcrystalline solids*

γ- (2-Thienyl)-γ-(4-hydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide (4a)

IR (KBr) : ν 3424, 1780, 1740, 1615, 1600, 1580 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.20 (1H, d, J = 7.1 Hz), 6.45-8.0 (8H, m). 4.1 (1H, s).

***γ- (5-Chloro-2-thienyl)-γ-(4-hydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (4b)**

IR (KBr): ν 3400, 1780, 1775, 1615, 1605, 1575 cm^{-1}; UV (Ethanol) : λ_{max} 260, 300, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.10 (1H, d, J = 7.2 Hz), 6. 50-8.0 (7H, m). 4.5 (1H, s).

***γ-(2-Thienyl)-γ-(2,4-dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (5a)**

IR (KBr): ν 3394, 1780, 1750, 1617, 1600, 1585 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 340 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.15 (1H, d, J = 7.2 Hz), 6.35-8.1 (7H, m). 4.50 (2H, br s).

***γ-(5-Chloro-2-thienyl)-γ-(2,4-dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (5b)**

IR (KBr): ν 3400, 1780, 1730, 1615, 1600, 1585 cm^{-1}; UV (Ethanol) : λ_{max} 260, 300, 340 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.10 (1H, d, J = 7.1 Hz), 6. 50-8.00 (6H, m). 4.1 (2H, br s).

***γ- (2-Thienyl)-γ-(3, 4 - dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$ - butenolide* (6a)**

IR (KBr): ν 3394, 1780, 1750, 1617, 1610, 1580 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 340 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.15 (1H, d, J = 7.0 Hz), 6.70-8.10 (7H, m). 4.50 (2H, br s).

***γ- (5-Chloro-2-thienyl)-γ-(3, 4-dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (6b)**

IR (KBr): ν 3422, 1780, 1730, 1620, 1605, 1590 cm^{-1}; UV (Ethanol) : λ_{max} 260, 310, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.20 (1H, d, J = 7.1 Hz), 6.70-7.95 (6H, m). 5.1 (2H, br s).

***γ-(2-Thienyl)-γ-(2, 5-dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (7a)**

IR (KBr): ν 3423, 1780, 1730, 1620, 1610, 1575 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 360 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.10 (1H, d, J = 7.1 Hz), 6.75-8.10 (7H, m). 5.50 and 5.60 (each 1H, s).

***γ-(5-Chloro-2-thienyl)-γ-(2, 5-dihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (7b)**

IR (KBr): ν 3409, 1780, 1730, 1617, 1600, 1585 cm^{-1}; UV (Ethanol) : λ_{max} 260, 310, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.15 (1H, d, J = 7.2 Hz), 6.70–8.15 (6H, m). 5.51 and 5.62 (each 1H, s).

***γ-(2-Thienyl)-γ-(2, 4, 6-trihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (8a)**

IR (KBr): ν 3300, 1785, 1740, 1618, 1590, 1580 cm^{-1}; UV (Ethanol) : λ_{max} 260, 300, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.20 (1H, d, J = 7.2 Hz), 6.65-8.0 (6H, m). 5.50, 5.55, 5.60 (each 1H, s).

***γ-(5-Chloro-2-thienyl)-γ-(2, 4, 6-trihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (8b)**

IR (KBr): ν 3400, 1780, 1750, 1620, 1600, 1585 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 360 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.20 (1H, d, J = 7.1 Hz), 6.69-8.0 (5H, m). 5.50, 5.53, 5.60 (each 1H, s).

***γ-(2-Thienyl)-γ-(2, 3, 4-trihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (9a)**

IR (KBr): ν 3400, 1780, 1740, 1625, 1605, 1590 cm^{-1}; UV (Ethanol) : λ_{max} 250, 320, 340 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.20 (1H, d, J = 7.1 Hz), 6.75-8.10 (6H, m). 5.60 (3H, br s).

***γ-(5-Chloro-2-thienyl)-γ-(2, 3, 4-trihydroxyphenyl)-$_{\Delta}^{\alpha\beta}$-butenolide* (9b)**

IR (KBr): ν 3400, 1785, 1735, 1618, 1600, 1585 cm^{-1}; UV (Ethanol) : λ_{max} 250, 300, 350 nm; ^{1}H NMR (80 MHz, DMSO-d_6) : δ 6.10 (1H, d, J = 7.1 Hz), 6.50–7.80 (5H, m). 5.55 (3H, br s).

5. CONCLUSIONS

A series of new γ,γ-disubstituted-$_{\Delta}^{\alpha\beta}$–butenolides of potential pharmacological properties are synthesized in 60 t0 75% yield by a simple and convenient protocol involving the use of easily accessible starting compounds. The method is economic as well as environmentally benign as it has been carried out without the use of any solvent.

ACKNOWLEDGEMENTS

The authors acknowledge their immeasurable gratitude to Professor P. C. Gupta for helpful encouragement. They also thank Head, SAIF, CDRI, Lucknow for providing analytical and spectral data. Financial support received from UGC, New Delhi is also thankfully acknowledged.

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