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**SHORT COMMUNICATION**

# SYNTHESIS OF NEW α,β-UNSATURATED BUTENOLIDES

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**ABSTRACT**. A number of new γ-substituted α,β-unsaturated butenolides have been synthesized by the condensation of phenols with β-(3-nitrobenzoyl)acrylic acid and β-(4-methyl-3-nitrobenzoyl)acrylic acid.

**KEY WORDS**: Butenolides, Aroylacrylic acids, Phenols

## INTRODUCTION

α,β-Unsaturated butenolides constitute an important family of five membered unsaturated γ-lactones which are commonly referred to as 2(5H)-furanones or α,β-butenolides. These compounds are well known for their antitumour, antifungal and antibacterial activities [1]. Some of them also occur in nature [2]. It is interesting to note that butenolides are often encountered among fungi [3], bacteria [4] and gorgonians [5], etc. The saturated analogues of these compounds are reported to act as signaling substances in bacteria [6] and enhance spore formation in streptomycetes or induce metabolite production [7]. There has been a continuous interest in the development of efficient and convenient methodologies for the synthesis of butenolides [8] because they are attractive building blocks in natural product synthesis and comprise structural moieties present in large number of significant compounds such as alkaloids [9], lignans [10], insect pheromones [11], cardenolides [2], flavour components [12] and large number of synthetic drug candidates with diverse biological activities [13]. These valid observations encouraged the authors to undertake the synthesis of some new substituted α,β-unsaturated butenolides **(4-11a**,**b)** by a simple and convenient method involving the use of easily accessible and inexpensive chemicals. The results of this synthetic venture are being reported in this communication. It is a well known fact that presence of electron withdrawing groups in the structures of β-arylacrylic acids augments the lactol formation, hence presence of nitro group is expected to increase the reactivity of these acids towards the phenols.

## EXPERIMENTAL

All melting points (°C) are uncorrected and TLC was used to access the reaction and purity of the compounds. IR spectra were recorded in KBr on Perkin-Elmer RX 1 spectrophotometer (USA). The $^1$H NMR spectra were measured in DMSO-$d_6$ solutions on a DRX-300 MHz spectrometer (Bruker, UK) using TMS as internal standard. UV spectra were recorded in methanol on a Perkin-Elmer Lambda 15 UV/Vis spectrophotometer (USA). The chemicals and solvents were procured from Sigma-Aldrich and E. Merck (Germany).

The synthesis of β-(3-nitrobenzyol)acrylic acid **(1a)** and β-(4-methyl-3-nitrobenzyol)acrylic acid **(1b)** was carried out by a literature procedure [14]. The phenols **(3a-f)** (phenol, resorcinol, catechol, quinol, phloroglucinol and pyrogallol) were taken in slight excess over the acid **(1)**.

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*Syntheses of compound **4-9a,b***

*Typical synthesis of 4-(2,4-dihydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**5a**).* The acid **1a** (4.42 g, 20 mmol) was intimately mixed with resorcinol (2.75 g, 25 mmol) and the resulting mixture was heated to 120 $^{o}$C to get a homogeneous solution. Thereafter, concentrated sulfuric acid (3 drops) was added and heating was continued between 120 and 130 $^{o}$C for 3.5 h to give a hard and brittle mass on cooling. The condensed mass was crushed, washed thoroughly with water to remove excess of resorcinol, extracted with 2% aqueous sodium hydroxide and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid to precipitate the butenolide. It was purified by column chromatography on a silica gel column using benzene-ethanol (80:20) as eluent. The eluted butenolide was crystallized from aqueous ethanol to get a light brown microcrystalline solid (4.6 g, 65%), m.p. 231-232 $^{o}$C, IR (KBr): 3425, 1790, 1750, 1614, 1550, 1370 cm$^{-1}$; UV: 260, 280 nm; $^{1}$H NMR: δ 5.6 (2H, br s), 6.1 (1H, d, J = 7.0 Hz), 6.8-8.1 (8H, m). Anal. found: C, 61.28; H, 3.70; N, 4.66%. Calcd. for $C_{16}H_{11}NO_6$: C, 61.34; H, 3.51, N, 4.47%. Rest of the butenolides were synthesized in identical manner as described above and their relevant data are given below.

*4-(4-Hydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**4a**).*Yellowish brown microcrystals (3.3 g, 50%), m.p. 180-182 $^{o}$C, IR (KBr) $\nu_{max}$: 3435, 1780, 1760, 1625, 1540, 1360 cm$^{-1}$; UV $\lambda_{max}$: 250, 270 nm; $^{1}$H NMR (DMSO-$d_6$) δ: 5.0 (1H,s), 6.1 (1H,d, J = 7.0 Hz), 7.0-8.1 (9H, m). Anal. found: C, 64.84; H, 3.62; N, 4.80%. Calcd. for $C_{16}H_{11}NO_5$: C, 64.64; H, 3.70; N, 4.71%.

*4-(4-Hydroxyphenyl)-4-(4-methyl-3-nitrophenyl)but-2-enolide (**4b**).* Brown microcrystals (3.3 g, 54.5%), m.p. 190-192 $^{o}$C, IR (KBr): 3450, 1780, 1760, 1625, 1560, 1350 cm$^{-1}$; UV: 240, 270 nm; $^{1}$H NMR: δ 2.25 (3H, s), 5.0 (1H, s), 6.2 (1H, d, J = 7.2 Hz), 6.8-8.2 (8H, m). Anal. found: C, 65.68; H, 4.09; N, 4.60%. Cacld. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.18; N, 4.50%.

*4-(2,4-Dihydroxyphenyl)-4-(4-methyl-3-nitropheny)but-2-enolide (**5b**).* Light brown microcrystalline solid (4.2 g, 64.2 %), m.p. 235-236 $^{o}$C, IR (KBr): 3400, 1780, 1740, 1620, 1555, 1340 cm$^{-1}$; UV: 243, 275 nm; $^{1}$H NMR: δ 2.20 (3H, s), 5.5 (2H, br s), 6.1 (1H, d, J = 7.1 Hz), 6.9-8.0 (7H, m). Anal. found: C, 62.56; H, 4.02; N, 4.40%. Cacld. for $C_{17}H_{13}NO_6$: C, 62.38; H, 3.97: N, 4.28 %.

*4-(3,4-Dihydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**6a**).* Brown microcrystals (4.3 g, 62.2 %), m.p. 195-196 $^{o}$C, IR (KBr): 3450, 1790, 1740, 1620, 1560, 1340 cm$^{-1}$; UV: 240, 280 nm; $^{1}$H NMR: δ 5.3 (2H, br s), 6.15 (1H, d, J = 7.0 Hz), 6.75-8.1 (8H, m). Anal. found: C, 60.55; H, 3.59; N, 4.56%. Cacld. for $C_{16}H_{11}NO_6$: C, 61.34; H, 3.51; N, 4.47%.

*4-(3,4-Dihydroxyphenyl)-4-(4-methyl-3-nitrophenyl)but-2-enolide (**6b**).* Brown crystalline solid (4.0 g, 60 %), m.p. 168-170 $^{o}$C, IR (KBr): 3450, 1790, 1740, 1620, 1560, 1350 cm$^{-1}$; UV: 240, 280 nm; $^{1}$H NMR: δ 2.21 (3H, s), 5.2 (2H, br s), 6.2 (1H, d, J = 7.2 Hz), 6.7-8.0 (7H, m). Anal. found: C, 62.51; H, 4.10; N, 4.30%. Cacld. for $C_{17}H_{13}NO_6$: C, 62.38; H, 3.97; N, 4.28%.

*4-(2,5-Dihydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**7a**).* Brown microcrystalline solid (4.2 g, 60 %), m.p. 226-228 $^{o}$C, IR (KBr): 3410, 1790, 1750, 1620, 1570, 1340 cm$^{-1}$; UV: 230, 275 nm; $^{1}$H NMR: δ 5.0 (2H, br s), 6.08 (1H, d, J = 7.0 Hz), 6.9-8.1 (8H, m). Anal. found: C, 60.45; H, 3.52; N, 4.52%. Cacld. for $C_{16}H_{11}NO_6$: C, 61.34; H, 3.51; N, 4.47%.

*4-(2,5-Dihydroxyphenyl)-4-(4-methyl-3-nitrophenyl)but–2-enolide (**7b**).* Dark brown crystals (3.80 g, 58%), m.p. 234-236 $^{o}$C, IR (KBr): 3450, 1780, 1730, 1615, 1560, 1335 cm$^{-1}$; UV: 250,

300 nm; $^1$H NMR: δ 2.15 (3H, s), 5.1 (2H, br s), 6.1 (1H, d, J = 7.2 Hz), 6.9-8.1 (7H, m). Anal. found: C, 62.53; H, 3.92; N, 4.17%. Calcd. for $C_{17}H_{13}NO_6$: C, 62.38; H, 3.97; N, 4.28%.

*4-(2,4,6-Trihydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**8a**).* Reddish brown microcrystalline compound (5.24 g, 70%), m.p. 205-207 °C, IR (KBr): 3430, 1790, 1740, 1625, 1550, 1350 cm$^{-1}$; UV: 240, 285 nm; $^1$H NMR: δ 5.8 (3H, br s), 6.2 (1H, d, J = 7.0 Hz), 6.85-8.0 (7H, m). Anal. found: C, 58.55; H, 3.39; N, 4.40%. Calcd. for $C_{16}H_{11}NO_7$: C, 58.35; H, 3.34; N, 4.25%.

*4-(2,4,6-Trihydroxyphenyl)-4-(4-methyl-3-nitrophenyl)but-2-enolide (**8b**).* Dark orange crystalline solid (4.9 g, 72%), m.p. 160-162 °C, IR (KBr): 3470, 1780, 1740, 1620, 1570, 1340 cm$^{-1}$; UV: 250, 275 nm; $^1$H NMR: δ 2.15 (3H, s), 5.5(3H, br s), 6.1 (1H, d, J=7.2 Hz), 6.7-8.0 (6H, m). Anal. found: C, 59.50; H, 3.77;N, 4.15%. Calcd. for $C_{17}H_{13}NO_7$: C, 59.47; H, 3.79; N, 4.08%.

*4-(2,3,4-Trihydroxyphenyl)-4-(3-nitrophenyl)but-2-enolide (**9a**).* Dark brown crystals (5.0 g, 64%), m.p. 207-209 °C, IR (KBr): 3430, 1780, 1740, 1625, 1540, 1350 cm$^{-1}$; UV: 260, 290 nm; $^1$H NMR: δ 5.5 (3H, br s), 6.25 (1H, d, J = 7.2 Hz), 6.8-8.1 (7H, m). Anal. found: C, 58.29; H, 3.28; N, 4.30%. Calcd. for $C_{16}H_{11}NO_7$: C, 58.35; H, 3.34; N, 4.25%.

*4-(2,3,4-Trihydroxyphenyl)-4-(4-methyl-3-nitrophenyl)but-2-enolide (9b).* Dark brown microcrystals (4.1 g, 62.7%), m.p. 215-216 °C, IR (KBr): 3450, 1790, 1620, 1750, 1560 cm$^{-1}$; UV: 260, 290 nm; $^1$H NMR: δ 2.15 (3H, s), 5.1 (3H, br s), 6.09 (1H, d, J = 7.2 Hz), 6.75-8.2 (6H, m). Anal. found: C, 59.64; H, 3.81; N, 4.20%. Calcd. for $C_{17}H_{13}NO_7$: C, 59.47; H, 3.79; N, 4.08%.

*Acetylation of butenolides **5a, 5b** (synthesis of **10a**,**b**)*

A mixture of the butenolide **5a** or **5b** (1.0 g, 3.2 or 3.1 mmol), acetic anhydride (20 mL, 212 mmol) and fused sodium acetate (2.0 g) was refluxed at 130-140 °C, for 3 h to afford diacetyl derivatives **10a** or **10b.** These were chromatographed on silica gel column using 10% acetone in pet ether as eluent. The eluted compound was further purified by crystallization with aqueous acetone to afford light yellow crystalline solids **10a** or **10b**. Their analytical data are as follows: **10a** (yield 0.9 g, 71.4%), m.p. 245-246 °C; IR (KBr): 1790, 1760, 1620, 1550, 1335 cm$^{-1}$; UV: 240, 270 nm; $^1$H NMR: δ 2.49 (6H,s), 6.1 (1H, d, J = 7.2 Hz), 6.8-8.1 (8H, m); Anal. found: C, 61.60; H, 3.41; N, 3.65%. Cacld. for $C_{20}H_{15}NO_8$: C, 60.45; H, 3.37; N, 3.52%). **10b** (0.9 g, 72%), m.p. 250-251 °C; IR (KBr): 1790, 1760, 1615, 1540, 1340 cm$^{-1}$; UV: 245, 270 nm; $^1$H NMR: δ 2.25 (3H, s), 2.49 (6H, s), 6.1 (1H, d, J = 7.2 Hz), 6.9-8.0 (7H, m). Anal. found: C, 61.29; H, 4.18; N, 3.61%. Calcd. for $C_{21}H_{17}NO_8$: C, 61.31; H, 4.13; N, 3.40%.

*Bromination of butenolides **5a, 5b** (synthesis of compounds **11a**,**b**)*

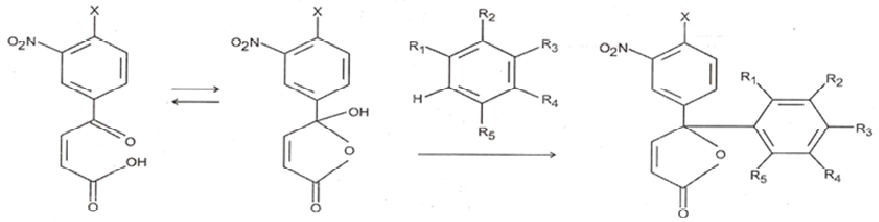
A solution of butenolide **5a** or **5b** (1.0g, 3.2 or 3.1 mmol) in glacial acetic acid (15 mL, 263 mmol) was treated with cooling and stirring with bromine (1 mL, 194 mmol) dissolved in glacial acetic acid (10 mL). The contents on dilution with water deposited a red-brown solid. It was chromatographed on a column of silica gel using benzene-ethanol (80:20) as eluent. The eluted compound was crystallized from acetic acid to get the brick-red microcrystals of dibromo compound **11a** (0.75 g, 50%, m.p. 258-260 °C) or **11b** (0.8 g, 54%, m.p. 262-264 °C). Their analytical data are as follows. **11a**: IR (KBr): 3400, 1780, 1750, 1620, 1540, 1350 cm$^{-1}$; UV: 240, 270 nm; $^1$H NMR: δ 5.5 (2H, br s), 6.2 (1H, d, J = 7.0 Hz), 6.7-8.1 (6H, m); Anal. found: C, 40.58; H, 1.93; N, 3.12; Br, 3.40%. Cacld. for $C_{16}H_9NO_6Br_2$: C, 40.76; H, 1.91; N, 2.97; Br

3.38%). **11b**: IR (KBr): 3400, 1780, 1750, 1648, 1620, 1345 $cm^{-1}$; UV: 250, 280 nm; $^1H$ NMR: δ 2.25 (3H,s), 5.6 (2H, br s), 6.08 (1H, d, J = 7.0 Hz), 6.8-8.1 (5H, m). Anal. found: C, 42.15; H, 3.31; N, 2.96; Br, 3.31%. Cacld. for $C_{17}H_{11}NO_6Br_2$: C, 42.46; H, 2.26; N, 2.88; Br, 3.29%.

Some of the synthesized compounds are under investigation for their antibacterial and antifungal activities. The results related with this study will be published elsewhere in near future.

## RESULTS AND DISCUSSION

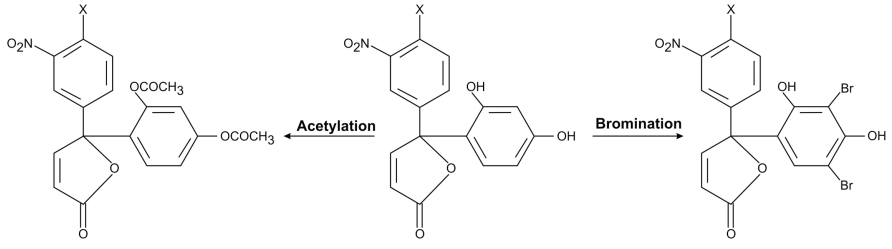
In the present work we have condensed two γ-keto acids, β-(3-nitrobenzoyl)acrylic acid **(1a)** and β-(4-methyl-3-nitrobenzoyl)acrylic acid **(1b)** with various mono-, di- and trihydroxyphenols in presence of catalytic quantity of concentrated sulfuric acid to get new α,β-unsaturated butenolides **(4-9a**,**b)**. The acids **(1a** and **1b)** reacted with phenols **(3a-f)** through their cyclic lactol tautomeric form **(2a** and **2b)** as shown in Scheme 1. The butenolides **5a**,**b** on acetylation and bromination afforded diacetyl (**10a**,**b**) and dibromo (**11a**,**b**) derivatives, respectively as given in Scheme 2.




**1** **2** **3** **4-9**

**3a**, **4**: $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$
**3b**, **5**: $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OH$
**3c**, **6**: $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = OH$
**3d**, **7**: $R_2 = R_3 = R_5 = H$; $R_1 = R_4 = OH$
**3e**, **8**: $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = OH$
**3f**, **9**: $R_4 = R_5 = H$; $R_1 = R_2 = R_3 = OH$
**1a**, **2a**, **4-9a** (X = H) and **1b**, **2b**, **4-9b** (X = Me)

Scheme 1. Synthesis of butenolides.




**10a-b** **5a-b** **11a-b**

**5a, 10a, 11a ) X = H and 5b, 10b, 11b) X = Me**

Scheme 2. Synthesis of butenolides **10a**,**b** and **11a**,**b**.

The occurrence of keto-lactol tautomerism in γ-keto acids and their participation in some chemical reactions through the cyclic lactol form is well documented [15]. In the synthesized compounds **(4-11a**,**b)** γ-carbon atom is attached to two different phenyl rings, one being

phenolic and other non-phenolic. Their structures are established on the basis of microanalysis, UV, IR, $^1$H NMR spectral data, and chemical reactions, e.g. acetylation and bromination.

The IR spectra (in KBr) of the butenolides **4-9a**,**b** and **11a**,**b** showed a broad and strong absorption band in the region 3400-3470 $cm^{-1}$ due to bonded OH stretching vibrations. The diacetyl compounds **10a**,**b** did not exhibit any absorption in hydroxyl region. All the butenolides **(4-11a**,**b)** displayed sharp and strong bands near 1730-1760 $cm^{-1}$ and 1780-1790 $cm^{-1}$ which are characteristics of five membered α,β-unsaturated-γ-lactone ring (νCO). A sharp peak at 1614-1625 was attributed to the vibrations of olefinic double bond (νC=C) present in all the structures. The UV spectra (in methanol) of all the butenolides revealed the same pattern of absorption at 240-260 nm and 270-300 nm. In the $^1$H NMR spectra (DMSO-$d_6$) of the butenolides, α-olefinic proton appeared as a doublet at δ 6.08-6.25 while the β-olefinic proton and aromatic protons formed a complex multiplet in the region between δ 6.7-8.2.

## CONCLUSIONS

In summary, we have synthesized a new series of butenolides in 50 to 72% yield by a simple and one step method. Besides having the advantages of simplicity and use of easily accessible starting materials, this method is environmentally benign as it does not employ any solvent.

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