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Note

Synthesis of some new $\Delta^{\alpha\beta}$ butenolides

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The synthesis of some new $\Delta^{\alpha\beta}$ butenolides has been accomplished by the condensation of two γ-keto acids, β-(4-acetamidobenzoyl)acrylic acid and β-(4-acetamido-3-nitrobenzoyl)acrylic acid with phenols using concentrated sulphuric acid as condensing agent.

Keywords: Butenolides, aroylacrylic acids, phenols

$\Delta^{\alpha\beta}$Butenolides constitute a prominent family of five membered αβ-unsaturated γ-lactones which are also known as 2(5*H*)-furanones. These compounds are well known for their diverse biological activities[1]. There has been a continuous interest in the development of efficient and convenient methodologies for the synthesis of butenolides[2] because they are attractive building blocks in natural product synthesis and comprise structural moieties present in large number of significant compounds such as alkaloids[3], lignans[4], insect pheromones[5], cardenolides[6], flavour components[7], and large number synthetic drug candidates[8-14].

In view of the above mentioned findings and the report of good bioactivity associated with acylamide agents[15,16], a number of new $\Delta^{\alpha\beta}$ butenolides **4-11** have been synthesized by condensing two γ-keto acids, β-(4-acetamidobenzoyl)acrylic acid **1a** and β-(4-acetamido-3-nitrobenzoyl)acrylic acid **1b** with various phenols **3** in presence of catalytic quantity of concentrated sulphuric acid. The method is simple and requires easily accessible inexpensive chemicals. The acids **1a** and **1b** reacted with phenols **3** through their cyclic tautomeric lactol form **2a** and **2b** as shown in **Scheme I**. Occurrence of keto-lactol tautomerism in γ-keto acids and their cyclization to lactol form in many chemical reactions is well documented[17]. In the synthesized butenolides **4-11** the γ-carbon atom is attached to two different phenyl rings, one being phenolic and the other non-phenolic containing acetamido group. Their structures are established by elemental analysis, UV-Vis, IR, NMR spectral data and chemical reactions *viz,* acetylation and bromination reactions.

All the synthesized butenolides **4-11** in their IR spectra (in KBr, ν_{max} in cm^{-1}) showed two sharp and strong bands near 1770-1790 and 1730-1760 which are characteristic of five membered αβ-unsaturated γ-lactone ring (νCO). A prominent peak noticed at 1615-1620 is assignable to olefinic double bond (ν C=C) present in lactonic ring. UV-Vis spectra (in methanol) revealed the presence of two absorption bands at 240-260 and 285-300 nm. In the ^{1}H NMR spectra (in DMSO-d_6) of the butenolides, α-olefinic proton appeared as a doublet at δ 6.09-6.20 while the β-olefinic proton and aromatic protons formed a complex multiplet in the region between δ 6.60 and 8.20.

Experimental Section

Melting points are uncorrected and TLC was used to monitor the progress of the reactions, and homogeneity of the compounds. The synthesis of β-(4- acetamidobenzoyl)acrylic acid **1a** was carried out by a literature procedure[18] and β-(4-acetamido-3-nitrobenzoyl)acrylic acid **1b** was synthesized by nitration of **1a**. The phenols (phenol, resorcinol, catechol, quinol, phloroglucinol, and pyrogallol) were taken in slight excess over the acid **1**.

Synthesis of β-(4-acetamido-3-nitrobenzoyl)-acrylic acid, 1b: The acid **1a** (22.3 g) was dried well, finely powdered and added slowly in small instalments with stirring to fuming nitric acid (100 mL) cooled to 0°C. The contents were allowed to stand for 15 min at 0-3°C and filtered through glass-wool into ice-cold water (600 mL). The acid **1b** separated out as a yellow solid. It was purified by recrystallization from ethanol. Yield, 21.6 g (78%), m.p. 248-49°C, IR (KBr): 3300, 1785, 1750, 1700,

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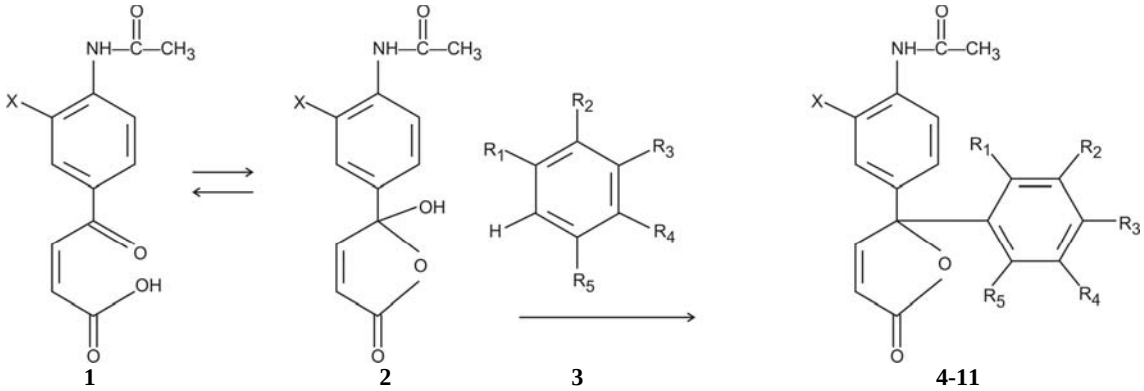

1 **2** **3** **4-11**

4: $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$
5: $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OH$
6: $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = OH$
7: $R_2 = R_3 = R_5 = H$; $R_1 = R_4 = OH$
8: $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = OH$
9: $R_4 = R_5 = H$; $R_1 = R_2 = R_3 = OH$
10: $R_2 = R_4 = R_5 = H$; $R_1 = R_3 = OCOCH_3$
11: $R_5 = H$; $R_2 = R_4 = Br$; $R_1 = R_3 = OH$

1 -11: **a**, X = H
b, X = NO_2

Scheme I

1662, 1620, 1610, 1340 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.03 (s, 3H), 6.60 and 6.81 (each 1H, d), 7.25-8.05 (m, 3H), 9.92 (s, 1H), 10.5 (s, 1H). Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.79; H, 3.59; N, 10.07. Found: C, 51.58; H, 3.66; N, 10.12%.

Synthesis of γ-(4-acetamidophenyl)-γ-(2, 4-dihydroxyphenyl)- $\Delta^{\alpha\beta}$butenolide, 5a: The acid, **1a** (4.66 g, 20 mmoles) and resorcinol (2.75 g, 25 mmoles) were intimately mixed with each other and the resulting mixture was heated to 140°C to obtain a homogeneous solution. Conc. H_2SO_4 (4 drops) was then added and heating continued between 140° and 150°C for 2.5 hr. The hard and brittle condensed mass was crushed and washed thoroughly with water to remove excess of resorcinol. It was extracted with 2% aq NaOH, and filtered. The filtrate was cooled in ice-cold water and acidified with dil HCl to afford the butenolide **5** as a sticky solid. The solid was purified by column chromatography over a silica gel column using benzene:ethanol (80:20) as eluent. The eluted compound was finally purified by recrystallization from aq ethanol to get brick-red microcrystals (4.46 g, 65%), m.p. 231-34°C; IR (KBr): 3300, 1790, 1750, 1660, 1620, 1610 cm^{-1}; UV-Vis (MeOH): 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.03 (s, 3H), 5.8 (br s, 2H), 6.2 (d, 1H), 6.60-8.0 (m, 8H), 8.9 (s, lH). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.62; N, 4.31. Found: C, 65.61; H, 4.52; N, 4.34%.

Rest of the butenolides were prepared in an identical manner as described above and their relevant data is given below.

4a: Yield 60%, m.p. 120-21°C; IR (KBr): 3378, 3280, 1780, 1760, 1670, 1625, 1610 cm^{-1}; UV-Vis (MeOH): 248, 295 nm; ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H), 4.9 (br s, 1H), 6.1 (d, 1H). 6.9-8.1 (m, 9H), 8.5 (s, 1H). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.90; H, 4.85; N, 4.53. Found: C, 70.23; H, 5.92; N, 4.61%.

4b: Yield 50%, m.p. 182-84°C; IR (KBr): 3410, 3200, 1780, 1750, 1655. 1620, 1610, 1530, 1340 cm^{-1}; UV-Vis (MeOH): 260, 295 nm; ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H), 5.25 (br s, 1H), 6.15 (d, 1H), 6.8-7.95 (m, 8H), 8.55 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.20; H, 3.95; N, 7.91. Found: C, 61.25; H, 4.10; N, 8.02%.

5b: Yield 66%, m.p. 198-200°C; IR (KBr): 3400, 3210, 1780, 1730. 1665, 1615, 1605, 1540, 1335 cm^{-1}; UV-Vis (MeOH): 260, 300 nm; ^1H NMR (DMSO-d_6): δ 2.08 (s, 3H), 5.0 (br s, 2H), 6.2 (d, IH), 6.75-7.98 (m, 7H), 8.7 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_7$: C, 58.38; H, 3.78; N, 7.57. Found: C, 58.20; H, 3.71: N, 7.60%.

6a: Yield 65%, m.p. 213-14°C; IR (KBr): 3365, 3200, 1790, 1750, 1660, 1620, 1610 cm^{-1}; UV-Vis (MeOH): 248, 290 nm; ^1H NMR (DMSO-d_6): δ 1.95 (s, 3H), 5.70 (br s, 2H), 6.15(d, 1H), 7.1-8.2 (m, 8H), 8.55 (s, 1H). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.67; H, 4.59; N, 4.40%.

6b: Yield 60%, m.p. 193-95°C; IR (KBr): 3300, 1780, 1740, 1660, 1615, 1610, 1545, 1330 cm^{-1}; UV-Vis (MeOH): 260, 300 nm; ^1H NMR (DMSO-d_6): δ 2.07 (s, 3H), 4.8 (br s. 2H), 6.23(d, 1H), 6.88-8.21 (m, 7H), 8.60 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_7$: C,

58.38; H, 3.78; N, 7.57. Found: C, 58.15; H, 3.68; N, 7.44%.

7a: Yield 70%, m.p. 228-30°C; IR (KBr): 3423, 3230, 1780, 1740, 1655, 1620, 1605 cm^{-1}; UV-Vis (MeOH): 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H). 5.0 (br s, 2H), 6.1 (d, 1H), 6.8-7.9 (m, 8H), 8.7 (s, 1H). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.10; H, 4.51; N, 4.28%.

7b: Yield 55%, m.p. 189-91°C; IR (KBr): 3400, 3200. 1780, 1730, 1662, 1615, 1610, 1550, 1350 cm^{-1}; UV-Vis (MeOH): 245, 295 nm; ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H), 5.5 (br s, 2H), 6.1 (d, 1H), 6.9-8.1 (m, 7H), 8.7 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_7$: C, 58.38; H, 3.78; N, 7.57. Found: C, 58.15; H, 3.80; N, 7.61%.

8a: Yield 70%, m.p. 235-37°C; IR (KBr): 3450, 3200, 1790, 1760, 1655, 1620, 1612 cm^{-1}; UV-Vis (MeOH): 250, 300 nm; ^1H NMR (DMSO-d_6): δ 1.95 (s, 3H), 5.2 (br s, 3H), 6.1 (d, 1H), 6.75-8.0 (m, 8H), 8.6 (s, 1H). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.40; N, 4.11. Found: C, 62.86; H, 4.33; N, 3.98%.

8b: Yield 60%, m.p. 201-03°C; IR (KBr): 3400, 3260, 1770, 1740, 1660, 1620, 1610, 1550, 1340 cm^{-1}; UV-Vis (MeOH) : 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.0 (s, 3H), 5.5 (br s, 3H), 6.1 (d, 1H), 6.9-8.1 (m, 7H), 8.7 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_8$: C, 55.96; H, 3.63; N, 7.25. Found: C, 55.72; H, 3.65; N, 7.30%.

9a: Yield 65%, m.p. 239-41°C; IR (KBr): 3300, 1780, 1760, 1670, 1618, 1610 cm^{-1} UV-Vis (MeOH): 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H), 5.0 (br s, 3H). 6.15 (d,1H), 6.95-8.1 (m, 7H), 8.6 (s, 1H). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.40; N, 4.11. Found: C, 63.74; H, 4.45; N, 4.20%.

9b: Yield 65%, m.p. 197-99°C; IR (KBr): 3400, 3200, 1790, 1750, 1660, 1620, 1605, 1550, 1340 cm^{-1}; UV-Vis (MeOH): 260, 285 nm; ^1H NMR (DMSO-d_6): δ 2.15 (s, 3H), 5.1 (br s, 3H), 6.09 (d, 1H), 7.1-8.01 (m, 6H), 8.6 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_8$: C, 55.96; H, 3.63; N, 7.25. Found: C, 56.12; H, 3.95; N, 7.36%.

Acetylation of butenolides 5a, 5b: The butenolide **5a** or **5b** (1 g) was mixed with acetic anhydride (20 mL) and fused sodium acetate (3.0 g) and the mixture was refluxed at 130-140°C for 3 hr to give diacetyl derivatives **10a** or **10b**. These were chromatographed over silica gel column using 10% acetone in pet ether as eluent. The eluted compound **10a** or **10b** was purified by recrystallization from acetone as yellow crystalline solid. **10a**: Yield 0.9 g, m.p. 121-22°C; IR (KBr): 3280, 1790, 1750, 1660, 1620, 1610 cm^{-1}; UV-Vis (MeOH): 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.06 (s, 3H), 2.20 (s, 6H), 6.13 (d, 1H), 6.7-8.0 (m, 8H), 8.9 (s, 1H). Anal. Calcd for $C_{22}H_{19}NO_7$: C, 65.55; H, 4.65; N, 3.42. Found: C, 65.80; H, 3.70; N, 3.48%.

10b: Yield 0.8 g, m.p. 159-60°C; IR (KBr): 3270, 1780, 1755. 1665, 1625, 1615, 1540, 1340 cm^{-1}; UV-Vis (MeOH): 240, 285 nm; ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H), 2.20 (s, 6H), 6.15 (d, 1H), 6.7-8.21 (m, 7H), 8.80 (s, 1H). Anal. Calcd for $C_{22}H_{18}N_2O_9$: C, 58.15; H, 3.96; N, 6.17. Found: C, 57.81; H, 3.89; N, 5.96%.

Bromination of butenolide 5a, 5b: The butenolide **5a** or **5b** (1.0 g) was dissolved in glacial acetic acid (25 mL) and the solution cooled. To it, 10% solution of bromine in glacial acetic acid (10 mL) was added dropwise with stirring and cooling. The contents were diluted with water to afford the orange-brown bromo compound **11a** or **11b**. It was chromatographed over a column of silica gel using benzene:ethanol (80:30) eluent. The eluted solid was purified by recrystallization from acetic acid.

11a: Yield 1.4 g, m.p. 251-53°C; IR (KBr): 3467, 3280, 1780, 1740, 1670, 1615, 1608 cm^{-1}; UV-Vis (MeOH) : 250, 300 nm; ^1H NMR (DMSO-d_6): δ 2.1 (s, 3H), 5.9 (br s, 2H), 6.2 (s, 1H), 6.85-7.90 (m, 6H), 8.75 (s, 1H). Anal. Calcd for $C_{18}H_{13}NO_5Br_2$: C, 44.72; H, 2.69; N, 2.89; Br, 33.12. Found: C, 44.56; H, 2.68; N, 2.92, Br, 33.30%.

11b: Yield 0.7 g, m.p. 208-10°C; IR (KBr): 3300, 1790, 1760, 1660, 1620, 1610, 1555, 1340 cm^{-1}; UV-Vis (MeOH): 260, 285 nm; ^1H NMR (DMSO-d_6): δ 2.09 (s, 3H), 5.75 (br, s, 2H), 6.10 (d. 1H). 7.1-8.1 (m, 5H), 8.80 (s, 1H). Anal. Calcd for $C_{18}H_{12}N_2O_7Br_2$: C, 40.90; H, 2.27; N, 2.65; Br, 30.30. Found: C, 41.25; H, 2.30; N, 2.71, Br, 30.26%.

Synthesized compounds are under evaluation for their antimicrobial activities and the related results will be published elsewhere in near future.

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