

SYNTHESIS OF AZETIDIN-2-ONES DERIVED FROM 7-ACETOXY-3-AMINO-2H-1-BENZOPYRAN-2-ONE

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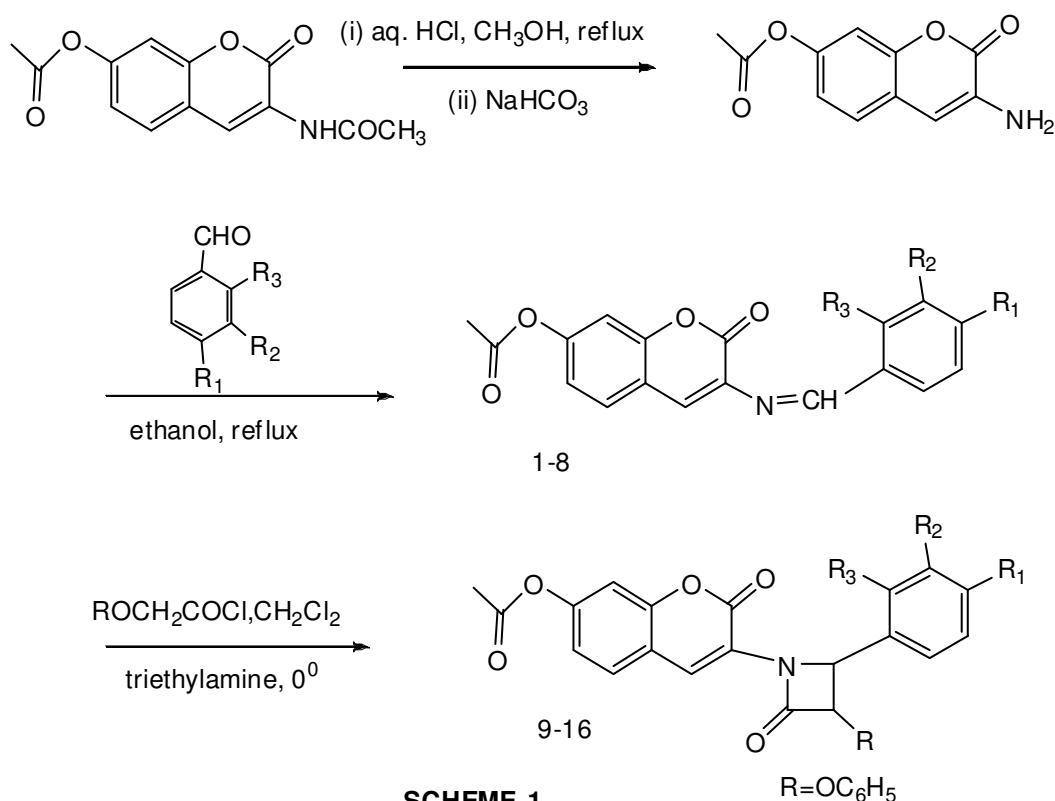
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Earlier we reported synthesis of psora-azetidin-2-one containing electron withdrawing groups. Herewith β -lactam ring formation is achieved containing electron withdrawing and electron releasing groups with formation of azetidin-2-ones derived from 7-acetoxy-3-amino-2H-1-benzopyran-2-one via corresponding Schiff bases.

The ancient Hindus, Turks, Egyptians and other orientals have exploited the property of derivatives of 2H-1-benzopyran-2-one in popular medicines by using plants or herbs for the treatment of vitiligo since ancient times. In 1948, El Mofty rationalized furo-fused 2H-1-benzopyran-2-one therapy by using the active components of *Ammi majus* (mainly 8-methoxy furo-fused 2H-1-benzopyran-2-one and 3-methoxy furo-fused 2H-1-benzopyran-2-one), isolated in chemically pure states¹.

Scientific interest in 2H-1-benzopyran-2-one has markedly grown over the last few decades after the clinical introduction of 8-methoxy furo-fused 2H-1-benzopyran-2-one followed by UV-irradiation in the treatment of Psoriasis by Parrish *et al.*²

Utility of azetidinones as synthones for various biologically active compounds as well as their recognition as cholesterol absorption inhibitor^{3,4} and enzyme inhibitor⁵ has been reported.



SCHEME-1

Table-1
Characterization data of compounds 1-16

| Entry | R ₁ | R ₂ | R ₃ | M.P. (°C) | Yield (%) |
|-------|-----------------|------------------|-----------------|--------------|--------------|
| 1 | NO ₂ | H | H | 191-192 | 62 |
| 2 | Cl | H | H | 182-183 | 66 |
| 3 | NO ₂ | H | NO ₂ | 218-219 | 75 |
| 4 | Cl | H | Cl | 205-206 | 75 |
| 5 | CH ₃ | H | H | 155-156 | 57 |
| 6 | OH | H | H | 188-189 | 53 |
| 7 | OH | H | OH | >250 | 57 |
| 8 | OH | OCH ₃ | H | 208-209 | 53 |
| 9 | NO ₂ | H | H | >250*dec. | 21 |
| 10 | Cl | H | H | >250*dec. | 25 |
| 11 | NO ₂ | H | NO ₂ | >250*dec. | 28 |
| 12 | Cl | H | Cl | >250*dec. | 29 |
| 13 | CH ₃ | H | H | 236-237 | 20 |
| 14 | OH | H | H | >250*dec. | 18 |
| 15 | OH | H | OH | >250*dec. | 16 |
| 16 | OH | OCH ₃ | H | >250*dec. | 12 |

In view of developing combining effect of β -lactam ring and 2*H*-1-benzopyran-2-one, we have synthesized azetidin-2-one derivatives derived from 7-acetoxy-3-amino 2*H*-1-benzopyran-2-one containing electron withdrawing groups such as chloro, nitro and electron releasing group such as methoxy, hydroxyl and methyl.

Experimental

Melting points were determined by capillary methods and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel using ultraviolet light and /or iodine vapour as visualizing agents. Compounds were purified by column chromatography using silica gel column. Elemental analysis was carried out on a Perkin-Elmer CHNS analyzer (Model-2400). Infrared spectra were recorded on a Perkin-Elmer-FTIR spectrophotometer (KBr discs). Proton magnetic resonance spectra were recorded on a Bruker 400 MHz spectrophotometer.

Synthesis of Schiff's bases 1-8 : General procedure

A mixture of 7-acetoxy-3-amino-2*H*-1-benzopyran-2-one **1** (0.5g, 0.0023 mol) and the substituted

benzaldehydes (0.0021 mol) in 20 ml of absolute ethanol with few drops of glacial acetic acid was refluxed for 24 hr. The completion of reaction was monitored by thin layer chromatography. Excess ethanol was then distilled off and the solid was purified by column chromatography using pet- ether-ethyl acetate mixture (80:20) and recrystallized from ethanol.

Synthesis of 9-16 : General procedure

A mixture of Schiff bases **1-8** (0.001 mol) in dichloromethane (0.005 mol) and triethylamine (0.001 mol) was prepared and chilled to 0°. To it there was added a solution of phenoxyacetylchloride (0.001 mol) in dichloromethane (0.0024 mol) dropwise with constant stirring while maintaining the temp. at 0°. This was followed by stirring the reaction mixture at room temp for about five hours. The progress of the reaction was monitored by TLC. The reaction mixture was then poured onto crushed ice (100 g) and stirred further for about 10 min. followed by removal of dichloromethane under reduced pressure. Filtration of the solid and purification by column chromatography furnished the corresponding azetidinones which were recrystallised from ethanol.

7-Acetoxy-3-(4'-nitrobenzalimino)-2H-benzopyran-2-one 1

IR(KBr) cm^{-1} : 3069, 2931, 1725, 1715, 1648, 1588, 1559, 1380, 1290, 1161, 1128, 822. PMR (400 MHz, CDCl_3) δ ppm: 2.46 (s, 3H, OCOCH_3), 7.50 (s, 1H), 7.65 (d, $J=8.4$ Hz, 2H), 7.75 (d, $J=7.9$ Hz, 1H), 7.83 (d, $J=7.9$ Hz, 1H), 7.86 (d, $J=8.4$ Hz, 2H), 8.31 (s, 1H), 9.03 (s, 1H, N=CHAr). [Found: C, 61.51, H, 3.75, N, 8.04 $\text{C}_{18}\text{H}_{12}\text{O}_6\text{N}$ requires C, 61.36, H, 3.40, N, 7.95].

7-Acetoxy-3-(4'-chlorobenzalimino)-2H-benzopyran-2-one 2

IR (KBr): 3038, 2969, 1722, 1710, 1678, 1571, 1407, 1368, 1128, 779. PMR (400 MHz, CDCl_3): 2.32 (s, 3H, OCOCH_3), 7.41 (s, 1H), 7.48 (d, $J=8.4$ Hz, 2H), 7.65 (d, $J=7.5$ Hz, 1H), 7.80 (d, $J=7.5$ Hz, 1H), 7.82 (d, $J=8.4$ Hz, 2H), 8.04 (s, 1H), 8.62 (s, 1H, N=CHAr). [Found: C, 63.51, H, 3.75, N, 4.44 $\text{C}_{18}\text{H}_{12}\text{ClO}_4\text{N}$ requires C, 63.25, H, 3.51, N, 4.09%].

7-Acetoxy-3-(2', 4'-dinitrobenzalimino)-2H-benzopyran-2-one 3

IR (KBr): 3054, 2991, 1724, 1715, 1638, 1576, 1558, 1443, 1380, 1264, 1128, 801, 791. PMR (400 MHz, CDCl_3): 2.37 (s, 3H, OCOCH_3), 7.41 (s, 1H), 7.66-7.70 (d, $J=7.5$ Hz and $J=8.4$ Hz, 2H), 7.75 (d, $J=7.5$ Hz, 1H), 7.80 (d, $J=8.4$ Hz, 1H), 7.84 (s, 1H), 8.04 (s, 1H), 8.89 (s, 1H, N=CHAr). [Found: C, 54.03, H, 2.64, N, 10.92 $\text{C}_{18}\text{H}_{11}\text{O}_8\text{N}_3$ requires C, 54.40, H, 2.77, N, 10.57%].

7-Acetoxy-3-(2', 4'-dichlorobenzalimino)-2H-benzopyran-2-one 4

IR (KBr): 3028, 2967, 1722, 1713, 1631, 1561, 1359, 1121, 789. PMR (400 MHz, CDCl_3): 2.33 (s, 3H, OCOCH_3), 7.48 (s, 1H), 7.53-7.76 (d, $J=7.5$ Hz and $J=8.31$ Hz, 2H), 7.78 (d, $J=7.5$ Hz, 1H), 8.04 (d, $J=8.31$ Hz, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 9.03 (s, 1H, N=CHAr). [Found: C, 57.21, H, 2.73, N, 3.90 $\text{C}_{18}\text{H}_{11}\text{Cl}_2\text{O}_4\text{N}$ requires C, 57.60, H, 2.93, N, 3.73%].

7-Acetoxy-3-(4'-methylbenzalimino)-2H-benzopyran-2-one 5

IR data (KBr): 3081, 2881, 2989, 1725, 1713, 1621, 1558, 1470, 1348, 1263, 1131, 784. PMR (400 MHz, CDCl_3): 2.24 (s, 3H, Ar- CH_3), 2.42 (s, 3H, OCOCH_3), 7.39 (s, 1H), 7.45 (d, $J=7.8$ Hz, 2H), 7.56 (d, $J=7.5$ Hz, 1H), 7.73 (d, $J=7.5$ Hz, 1H), 7.75 (d,

$J=7.8$ Hz, 2H), 7.83 (s, 1H), 8.92 (s, 1H, N=CHAr). [Found: C, 71.11, H, 4.75, N, 4.80 $\text{C}_{19}\text{H}_{15}\text{O}_4\text{N}$ requires C, 71.02, H, 4.67, N, 4.36%].

7-Acetoxy-3-(4'-hydroxybenzalimino)-2H-benzopyran-2-one 6

IR data (KBr): 3341, 3063, 2983, 1728, 1710, 1673, 1528, 1443, 1369, 1233, 1115, 865. PMR (400 MHz, CDCl_3): 2.91 (s, 3H, OCOCH_3), 6.94 (br, s, 1H, -OH), 7.39 (s, 1H), 7.47 (d, $J=7.9$ Hz, 2H), 7.65 (d, $J=7.5$ Hz, 1H), 7.92 (d, $J=7.5$ Hz, 1H), 7.84 (d, $J=7.9$ Hz, 2H), 8.06 (s, 1H), 9.30 (s, 1H, N=CHAr). [Found: C, 69.12, H, 4.35, N, 4.71 $\text{C}_{18}\text{H}_{13}\text{O}_5\text{N}$ requires C, 69.00, H, 4.15, N, 4.47%].

7-Acetoxy-3-(2', 4'-dihydroxybenzalimino)-2H-benzopyran-2-one 7

IR (KBr): 3374, 3053, 2918, 1715, 1709, 1627, 1531, 1464, 1347, 1141, 770. PMR (400 MHz, CDCl_3): 2.82 (s, 3H, OCOCH_3), 7.05 (br, s, 2H, -OH), 7.47 (s, 1H), 7.58-7.68 (d, $J=7.5$ Hz, and $J=8.3$ Hz, 2H), 7.75 (d, $J=7.5$ Hz, 1H), 7.93 (d, $J=8.3$ Hz, 1H), 8.13 (s, 1H), 8.40 (s, 1H), 9.21 (s, 1H, N=CHAr). [Found: C, 63.30, H, 3.57, H, 4.44 $\text{C}_{18}\text{H}_{13}\text{O}_6\text{N}$ requires C, 63.71, H, 3.83, N, 4.12%].

7 - A c e t o x y - 3 - (4 ' - h y d r o x y - 3 ' - methoxybenzalimino)-2H-benzopyran-2-one 8

IR (KBr): 3379, 3072, 2991, 2907, 1722, 1712, 1683, 1580, 1381, 1264, 1229, 1122, 856. PMR (400 MHz, CDCl_3): 2.73 (s, 3H, OCOCH_3), 4.80 (s, 3H, - OCH_3), 7.41 (br, s, 1H, -OH), 7.58 (s, 1H), 7.60-7.68 (d, $J=7.4$ Hz and $J=8.5$ Hz, 2H), 7.79 (d, $J=7.4$ Hz, 1H), 7.98 (d, $J=8.5$ Hz, 1H), 8.01 (s, 1H), 8.13 (s, 1H), 9.03 (s, 1H, N=CHAr). [Found: C, 64.44, H, 4.26, N, 4.17 $\text{C}_{19}\text{H}_{15}\text{O}_6\text{N}$ requires C, 64.58, H, 4.24, N, 3.96%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(4'-nitrophenyl)-3-phenoxyazetid-2-one 9

IR (KBr): 3027, 2910, 1746, 1728, 1715, 1632, 1560, 1434, 1209, 864. PMR (400 MHz, CDCl_3): 2.46 (s, 3H, CH_3), 3.81 (d, $J=10.0$ Hz, 1H, N-CH-), 5.52 (s, $J=10.0$ Hz, 1H, - $\text{COCH-OC}_6\text{H}_5$), 6.94-7.14 (m, 2H), 7.23 (s, 1H), 7.32-7.66 (m, 7H), 7.62 (d, $J=8.6$ Hz, 2H), 8.13 (d, $J=8.6$ Hz, 1H). [Found: C, 64.47, H, 3.81, N, 5.95 $\text{C}_{26}\text{H}_{18}\text{O}_8\text{N}_2$ requires C, 64.19, H, 3.70, N, 5.76%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(4'-chlorophenyl)-3-phenoxyazetid-2-one 10

IR (KBr): 3036, 2977, 1748, 1722, 1713, 1658, 1605, 1353, 843, 769. PMR (400 MHz, CDCl₃): 2.33 (s, 3H, CH₃), 3.72 (d, J=9.3 Hz, 1H, N-CH-), 5.43 (d, J=9.3 Hz, 1H, -CO-CH-OC₆H₅), 7.05-7.17 (m, 2H), 7.26 (s, 1H), 7.30-7.62 (m, 7H), 7.67 (d, J=8.6 Hz, 2H), 8.31 (d, J=8.6 Hz, 1H). [Found : C, 65.43, H, 3.69, N, 3.09 C₂₆H₁₈ClO₆N requires C, 65.61, H, 3.78, N, 2.94%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(2',4'-dinitrophenyl)-3-phenoxyazetid-2-one 11

IR data (KBr): 3045, 2926, 1756, 1728, 1724, 1675, 1561, 1533, 1227, 1137, 887. PMR (400 MHz, CDCl₃): 2.73 (s, 3H, CH₃), 4.35 (d, J=12.0 Hz, 1H, N-CH-), 5.86 (d, J=12.0 Hz, 1H, -CO-CH-OC₆H₅), 7.14-7.19 (m, 2H), 7.29 (s, 1H), 7.38-7.68 (m, 6H), 7.74 (s, 1H), 7.80 (s, 1H), 8.40 (d, J=8.6 Hz, 1H). [Found : C, 58.50, H, 3.45, N, 8.04 C₂₆H₁₇O₁₀N₃ requires C, 58.75, H, 3.20, N, 7.90%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(2',4'-dichlorophenyl)-3-phenoxyazetid-2-one 12

IR (KBr): 3054, 2925, 1747, 1722, 1710, 1632, 1236, 804, 741. PMR (400 MHz, CDCl₃): 2.25 (s, 3H, CH₃), 4.44 (d, J=10.0 Hz, 1H, N-CH-), 5.70 (d, J=10.0 Hz, 1H, -CO-CH-OC₆H₅), 6.93-7.13 (m, 2H), 7.19 (s, 1H), 7.23-7.50 (m, 6H), 7.62 (s, 1H), 7.92 (s, 1H), 8.13 (d, J=8.4 Hz, 1H). [Found : C, 61.41, H, 3.54, N, 2.97 C₂₆H₁₇Cl₂O₆N requires C, 61.29, H, 3.33, N, 2.75%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(2',4'-methylphenyl)-3-phenoxyazetid-2-one 13

IR (KBr): 3032, 2971, 1740, 1722, 1713, 1632, 1515, 1254, 844, 775. PMR (400 MHz, CDCl₃): 2.32 (s, 3H, Ar-CH₃), 2.46 (s, 3H, -OCOCH₃), 3.90 (d, J=8.4 Hz, 1H, N-CH-), 5.52 (d, J=8.4 Hz, 1H, -CO-CH-OC₆H₅), 6.84 (m, 2H), 7.05 (s, 1H), 7.10-7.23 (m, 7H), 7.41 (d, J=8.6 Hz, 2H), 8.04 (d, J=8.6 Hz, 1H). [Found : C, 71.31, H, 4.44, N, 3.18 C₂₇H₂₁O₆N requires C, 71.20, H, 4.61, N, 3.07%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(4'-hydroxyphenyl)-3-phenoxyazetid-2-one 14

IR data (KBr): 3333, 3063, 2971, 1756, 1722, 1712, 1650, 1560, 1253, 843, 769. PMR data (400 MHz, CDCl₃): 2.64 (s, 3H, -CH₃), 4.17 (d, J=9.3 Hz, 1H, N-CH-), 5.70 (d, J=9.3 Hz, 1H, -CO-CH-OC₆H₅),

6.60-6.84 (br, s, 1H), 6.85-6.94 (m, 2H), 7.19 (s, 1H), 7.23-7.77 (m, 7H), 7.92 (d, J=8.4 Hz, 2H), 8.22 (d, J=8.4 Hz, 1H). [Found : C, 68.40, H, 4.08, N, 3.45 C₂₆H₁₉O₇N requires C, 68.27, H, 4.15, N, 3.06%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(2',4'-dihydroxyphenyl)-3-phenoxyazetid-2-one 15

IR data (KBr): 3242, 3036, 2926, 1740, 1729, 1704, 1665, 1512, 1239, 840, 714. PMR (400 MHz, CDCl₃): 2.69 (s, 3H, CH₃), 4.71 (d, J=10.0 Hz, 1H, N-CH-), 6.06 (d, J=10.0 Hz, 1H, -CO-CH-OC₆H₅), 6.42-7.14 (br, s, 2H), 7.23-7.29 (m, 2H), 7.47 (s, 1H), 7.58-7.92 (m, 6H), 8.04 (s, 1H), 8.40 (s, 1H), 8.64 (d, J=8.6 Hz, 1H). [Found : C, 65.43, H, 4.08, N, 3.09 C₂₆H₁₉O₈N requires C, 65.96, H, 4.06, N, 2.95%].

1-(7-Acetoxy-2H-1-benzopyran-2-one-3-yl)-4-(4'-hydroxy-3'-methylphenyl)-3-phenoxyazetid-2-one 16

IR (KBr): 3378, 3072, 2925, 1747, 1722, 1713, 1666, 1533, 1263, 856, 705. PMR (400 MHz, CDCl₃): 2.60 (s, 3H, -CH₃), 4.08 (d, J=9.8 Hz, 1H, N-CH-), 4.71 (s, 3H, -OCH₃), 5.86 (d, J=9.8 Hz, 1H, -CO-CH-OC₆H₅), 6.50-6.76 (br, s, 1H), 6.81-7.14 (m, 2H), 7.32 (s, 1H), 7.41-7.82 (m, 6H), 7.19 (d, J=8.9 Hz, 2H), 8.31 (d, J=8.9 Hz, 1H). [Found : C, 66.33, H, 4.35, N, 2.98 C₂₇H₂₁O₈N requires C, 66.52, H, 4.31, N, 2.87%].

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