Knoevenagel Condensation Shadowed by Michael Addition & O-Alkylation of Resorcinol, Malononitrile and Benzaldehyde to form Pyrrolidine, Piperidine and Morpholine Substituted Benzopyran Derivatives in Dry K_2CO_3

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A condensation reaction of resorcinol, malononitrile and benzaldehyde in presence of sodium carbonate at room temperature on vigorous stirring gives 2-amino-7-hydroxy-4-phenyl-4H-1-benzopyran-3-carbonitrile which on alkylation in presence of dry potassium carbonate in dry acetone at 70-80 °C with 1,2-chloroethyl pyrrolidine, 1,2-chloroethyl piperidine, 1,2-chloroethyl morpholine gives corresponding novel compounds.

Keywords: Knoevenagel condensation, Michael addition, 1,2-Chloroethyl pyrrolidine, Piperidine, Morpholine.

INTRODUCTION

It is well known that one pot multicomponent reactions are always better than multi-step synthesis, as they require minimal workup and desired product can be obtained in one pot often in quantitative yields [1,2]. Water is easily available solvent, use of water as solvent in the organic synthesis give rise to green chemistry. It is less pollutant, non-hazardous, non-combustible solvent these properties of water promote it in organic synthesis [3,4]. We report pyridine, piperidine and morpholine substituted 2-aminobenzopyran moiety which is very active and possess many biological activities. Formation of this moiety undergone Knoevenagel condensation, in which malononitrile (an active methylene compound) react with benzaldehyde in presence of tracing amount of methanol and aqueous solution of sodium carbonate and formed benzyldine propane dinitrile on loss of a water molecule. A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compounds to a carbonyl group followed by dehydration reaction in which a molecule of water is eliminated [5,6]. Active hydrogen compounds *viz.* diethyl malonate, Meldrum's acid, ethylacetoacetate, malonic acid, cyanoacetic acid, malononitrile, *etc.* [7-9].

In the same multi-component reaction second turn of the reaction undergone by Michael addition, in which benzyldine propanedinitrile reacts with 1,3-resorcinol and to form [(2,4-dihydroxyphenyl)(phenyl)methyl]propane dinitrile which on cyclization and bond shifting formed 2-amino-7-hydroxy-4-phenyl-4H-1-benzopyran-3-carbonitrile [10]. Michael addition is appropriate to the larger class of conjugated addition and the most useful method for C-C bond formation. The Michael addition is thermodynamically controlled; the reaction donors are active methylene's such as malonates and nitroalkanes, and the acceptors are activated olefins such as α,β -unsaturated carbonyl compounds [11,12]. The second step reaction undergone O-alkylation in which 1,2-chloroethylpyrrolidine, 1,2-chloroethylpiperidine or 1,2-chloroethylmorpholine act as alkylating agent and -OH part of substrate alkylate and given ether as product. The alkyl group may be transferred as an alkyl carbocation, a free radical, carbanion or a carbene or their equivalents [13,14]. When the alkylating agent is an alkyl halide, the conversion is known as Williamson ether synthesis. Alcohols are also considered as good alkylating agents in the presence of suitable acid/base catalysts [15].

The interest in benzopyrans and their derivatives increased since many years because these compounds are components

of many naturally occurring products and have also been subjected to structural modifications for potential medicinal properties. 2-Amino-7-hydroxy-4-phenyl-4*H*-1-benzopyran-3-carbonitrile (**1a**) had reported as *in vitro* cytotoxic activity on a human breast tumor cell line (MCF7, IC₅₀ 8 nM) [16,17].

EXPERIMENTAL

Laboratory grade chemicals and solvents were purchased from Sigma Aldrich and Merck and used without any further purification. The reactions were monitored by TLC using Merck's silica gel 60F254 aluminium sheets. Infrared spectra were recorded neat on Agilent Cary 630 spectrophotometer. High resolution mass spectra were recorded on Agilent 6520 (Q-TOF). NMR spectra were recorded on a Bruker Avance 400 (FT NMR) DPX300MHz NMR spectrometer.

Synthesis of 2-amino-7-hydroxy-4-phenyl-4*H*-1-benzopyran-3-carbonitrile (1a**):** A mixture of benzaldehyde, malononitrile and resorcinol in 2:2:2 dissolved in 1 mL methanol in round bottom flask. A 20 mL solution of 10 % Na₂CO₃ was added in round bottom flask and the resulting suspension kept on vigorous stirring for 10 h at 25 °C. After the completion of reaction filter the solution and residue washed with water then cold methanol and dried in oven at 100 °C (Scheme-I).

2-Amino-4-phenyl-7-[2-(pyrrolidin-1-yl)ethoxy]-4*H*-1-benzopyran-3-carbonitrile (1b**):** A mixture of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene (**1a**) (0.264 g, 1 mmol), 1-(2-chloroethyl)pyrrolidine-HCl (0.255 g, 1.5 mmol) dry K₂CO₃ (0.276 g 2 mmol) dissolved in 25 mL dry acetone in 50 mL round bottom flask and refluxed the solution for 8 h at 60-70 °C. Cooled the solution at room temperature and work-up with ethyl acetate and water, evaporate the solvent with rotatory evaporator and collected the yellow crystalline compound. Monitored the compound by TLC with methanol and chloroform (5:5).

2-Amino-4-phenyl-7-[2-(piperidin-1-yl)ethoxy]-4*H*-1-benzopyran-3-carbonitrile (1c**):** A mixture of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene (**1a**) (0.264g, 1 mmol), 1-(2-chloroethyl)piperidine-HCl (0.276 g, 1.5 mmol) dry K₂CO₃ (0.276 g, 2 mmol) dissolved in 25 mL dry acetone in 50 mL round bottom flask and refluxed the solution for 8 h at 60-70 °C. Cooled the solution at room temperature and work-up with ethyl acetate and water, evaporate the solvent with rotatory evaporator and collected the bright pink crystalline compound. Monitored the compound by TLC with methanol and dichloromethane (DCM) (4:6)

2-Amino-4-phenyl-7-[2-(morpholin-1-yl)ethoxy]-4*H*-1-benzopyran-3-carbonitrile (1d**):** A mixture of 2-amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene (**1a**) (0.264 g, 1 mmol), 1-(2-chloroethyl)morpholine-HCl (0.279 g, 1.5 mmol) dry K₂CO₃ (0.276 g, 2 mmol) dissolved in 25 mL dry acetone in 50 mL round bottom flask and then refluxed the solution for 8 h at 60-70 °C. Cooled the solution at room temperature and workup with ethyl acetate and water, evaporate the solvent with rotatory evaporator and collect the yellow crystalline compound. Monitored the compound by TLC with methanol and dichloromethane (DCM) (4:6)

Spectral data of selected compounds

2-Amino-7-hydroxy-4-phenyl-4*H*-1-benzopyran-3-carbonitrile (1a**):** Yield 85 %; white amorphous solid, m.p. 230-235 °C; IR (KBr, ν_{max}, cm⁻¹): 3495 (R-OH), 3332(R-NH₂), 2193 (R-CN), 1652 (C=CN vinyl nitrile), 1588-1406 (C-C arom.); ¹H NMR (400 MHz, DMSO δ ppm): 9.76 (s, Ar-OH), 7.36-7.33 (t, *J* = 12 Hz), 7.26-7.20 (q, *J* = 8 Hz) 6.90-6.84 (t, *J* = 12 Hz) 6.55-6.52 (dd, *J* = 4 Hz), 6.478-6.472 (d, *J* = 2.4 Hz), 4.66 (s). ¹³C NMR (100.60 MHz, DMSO δ ppm): 160.23-160.20, 156.98, 148.82, 146.31, 129.88, 127.33, 126.62, 113.75, 112.34, (C-C arom.), 120.60 (CN), 102.14 (C=C vinylic), 56.28 (C-O). HRMS-EI (*m/z*) calcd. for C₁₆H₁₂N₂O₂: 264.2786, found 264.2886. Elemental analysis % calcd. (found): C 72.72 (72.69), H 4.58 (4.60), N 10.60 (10.60).

2-Amino-4-phenyl-7-[2-(pyrrolidin-1-yl)ethoxy]-4*H*-1-benzopyran-3-carbonitrile (1b**):** Yield 75 %; brown color solid, m.p. 265-272 °C; IR (KBr, ν_{max}, cm⁻¹): 3334 (R-NH₂), 2188 (R-CN), 1649 (-C=CN), 1579-1400 (C-C arom.), 1336 (-C-OR, OR = ethoxypyrrolidine); ¹H NMR (300 MHz, CDCl₃ δ ppm): 7.24-7.23 (t, *J* = 1.2 Hz), 7.21-7.20 (d, *J* = 1.5 Hz), 7.18 (s), 7.15-7.14 (t, *J* = 1.35), 7.13-7.12 (t, *J* = 5.4), 7.105-7.100 (d, *J* = 1.5 Hz), 6.76 (s), 6.73 (s), 6.54-6.53 (d, *J* = 2.4 Hz), 6.519-6.510 (d, *J* = 2.7 Hz), 6.47-6.46 (d, *J* = 2.7 Hz), 4.18 (s), 4.56 (s), 4.00-3.96 (t, *J* = 11.7 Hz), 2.83-2.79 (t, *J* = 11.7 Hz), 2.57-2.53 (t, *J* = 12.9 Hz), 1.96 (s), 1.89 (s), 1.77-1.68 (m, *J* = 7.5 Hz). ¹³C NMR (75.49 MHz, CDCl₃, δ ppm): 159.50, 158.67, 149.31, 145.06, 130.34, 129.31, 128.90, 128.02, 127.29, 120.26, 115.16, 112.25, 102.13, 77.65, 77.23, 67.29, 60.67, 59.29, 54.96, 54.72, 40.61, 23.60, 1.16. HRMS-EI (*m/z*) calcd. for C₁₆H₁₂N₂O₃: 361.43692; ESI-SCAN-MS: + 362.18. Elemental analysis % calcd. (found): C 73.11 (73.15), H 6.41 (6.45), N 8.16 (8.16).

2-Amino-4-phenyl-7-[2-(piperidin-1-yl)ethoxy]-4*H*-1-benzopyran-3-carbonitrile (1c**):** Yield 70 %; bright pink color

Where R= H,Br, OCH₃, OH R¹= H,OH,OCH₃ R²= Pyrrolidine, Piperidine, Morpholine

Scheme-I

solid, m.p. 275-280 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3350 (R-NH₂), 2240 (R-CN), 1639 (C=CN vinyl nitrile), 1589-1450 (C-C arom.), 1302 (C-OR, OR = ethoxypiperidine); ¹H NMR (300 MHz, CDCl₃ δ ppm): 7.26-7.24 (t, J = 3 Hz), 7.214-7.209 (d = 1.5), 7.189 (s), 7.15-7.14 (d, J = 3 Hz), 6.77 (s), 6.75 (s), 6.547-6.539 (d, J = 2.4 Hz), 6.519-6.510 (d, J = 2.7 Hz), 6.472-6.462 (d, J = 2.7 Hz), 4.819 (s), 4.565 (s), 4.009-3.966 (t, J = 6.9 Hz), 2.98 (s) 2.833-2.794 (t, J = 5.7 Hz), 2.576-2.533 (q, J = 6.45 Hz), 1.96 (s), 1.89 (s). ¹³C NMR (75.49 MHz, CDCl₃, δ ppm): 157.31, 155.55, 155.20, 131.06, 129.33, 129.10, 119.99, 115.16, 114.25, 104.25, 77.44, 77.23, 62.88, 61.86, 57.88, 55.09, 42.22, 34.55, 31.96. HRMS-EI (m/z) calcd. for C₂₃H₂₅N₃O₂: 375.4635; ESI-SCAN-MS: +376.09. Elemental analysis % calcd. (found): C 71.79 (71.83), H 6.43 (6.44), N 11.16 (11.19).

2-Amino-4-phenyl-7-[2-(morpholin-1-yl)ethoxy]-4H-1-benzopyran-3-carbonitrile (1d): Yield 68 %; yellow color solid; m.p. 275-280 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3335 (R-NH₂), 2198 (R-CN), 1644 (C=CN vinyl nitrile), 1599-1442 (C-C arom.), 1335 (C-OR, OR = ethoxymorpholine); ¹H NMR (300 MHz, CDCl₃ δ ppm): 7.255-7.241 (t, J = 4.2 Hz), 7.112-7.090 (d, J = 6.6 Hz), 7.009 (s), 6.990-6.987 (d, J = 0.9 Hz), 6.88 (s), 6.76 (s), 6.455-6.454 (d, J = 0.3 Hz), 6.424-6.420 (d, J = 1.2 Hz), 4.908 (s), 4.670 (s), 4.098-4.086 (t, J = 3.6 Hz), 2.992 (s), 2.883-2.862 (t, J = 6.3 Hz), 2.588-2.537 (q, J = 7.65 Hz), 2.003 (s), 1.962 (s), 1.884 (s). ¹³C NMR (75.49 MHz, CDCl₃, δ ppm): 159.66, 156.31, 153.55, 152.20, 135.96, 129.33, 129.10, 120.99, 115.16, 114.85, 104.25, 77.98, 77.23, 65.88, 61.86, 57.88, 55.70, 42.22, 39.33, 35.65, 31.22. HRMS-EI (m/z) calcd. for C₂₂H₂₃N₃O₃: 377.43632; ESI-SCAN-MS: +377.47509. Elemental analysis % calcd. (found): C 70.01 (70.83), H 6.14 (6.22), N 11.13 (11.15).

2-Amino-4-(3-bromophenyl)-7-hydroxy-4H-1-benzopyran-3-carbonitrile (2a): Yield 80 %; off white color solid; m.p. 265-270 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3443 (R-OH), 3335 (R-NH₂), 2192 (R-CN), 1640 (C=CN, vinyl nitrile), 1587-1410, (C-C arom.), 720 (R-C-Br); ¹H NMR (400 MHz, DMSO δ ppm): 8.35 (s), 7.47-7.39 (t, J = 22 Hz), 7.35-7.31 (t, J = 16 Hz), 7.24-7.22 (d, J = 8 Hz), 6.99 (s), 6.88-6.86 (d, J = 8 Hz), 6.577-6.480 (ddd, J = 2.4 Hz), 4.73 (s). ¹³C NMR (100.60 MHz, DMSO δ ppm): 160.34, 160.30, 157.20, 149.06, 148.78, 130.89, 129.94, 129.88, 129.58, 126.55, 121.81, 120.412, 112.97, 112.51, 102.24, 55.65. HRMS-EI (m/z) calcd. for C₁₆H₁₁N₂O₂Br, 343.1747, found 343.1751. Elemental analysis % calcd. (found): C 56.00 (56.11), H 3.23 (3.26), N 8.16 (8.15).

RESULTS AND DISCUSSION

In the present work, a multi component reaction in which active methylene compounds (malononitrile) reacted with carbonyl compounds (benzaldehyde and substituted benzaldehyde) in presence of tracing amount of methanol and weak basic medium (aq. Na₂CO₃) and formed benzylidene propanedinitrile. The benzylidene propanedinitrile reacted with resorcinol and formed [(2,4-dihydroxyphenyl)(phenyl)methyl]propanedinitrile which on cyclization given 7-hydroxy-2-imino-4-phenyl-3,4-dihydro-2H-1-benzopyran-3-carbonitrile by hydrogen shift it converted into 2-amino-7-hydroxy-4-phenyl-4H-1-benzopyran-3-carbonitrile. In the second step, above formed

compounds reacted with pyrrolidine, piperidine and morpholine substituted alkyl halide, in presence of dry. K₂CO₃ and dry acetone as medium to form novel benzopyran derivatives. Simple reaction conditions and easy available catalyst made it favourable for synthesis in high yields.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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