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Synthesis of new potential Indole-3-yl derivatives via Knoevenagel condensation

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Abstract: A variety of 1-acetyl-1H-indol-3-yl derivatives have been prepared from indole-3-carboxaldehyde. By knoevenagel reaction between indole-3-carboxaldehyde and active methylene or non-active methylene compounds yielded the coresponding condensation product, indole-3-yl derivatives (**2a-e**) and then their N-acetylation with acetyl chloride afforded N-acetyl-1H-indol-3-yl derivatives (**3a-e**). ^{1}H-NMR, LC-MS, FT-IR and UV-Visible tools were used to confirm the structures.

Keywords: Indole-3-carbaxaldehyde; 3-substituited indole derivatives; knoevenagel reaction; acetylation.

1. Introduction

Indole nucleus is one of the most important alkaloid molecule found extensively in biological system and it has become an important structural component in many synthetic pharmaceuticals.[1-3] By using intermolecular and intramolecular approaches, number of various methods have been accepted to synthesis the indole based compounds [4-6] and it has gained its importance in medicinal chemistry due to its multidirectional biological activities such as antimicrobial,[7-9] anticancer, antioxidant,[10-12] antipyretic, analgesic, anti-inflammatory, [13] enzyme inhibitors and receptor antagonist.[14,15]

Among the different positions of indole ring, the C-3 position is preferred for electrophilic substitution and they are versatile intermediates for the synthesis of different compounds.[16] Some of the C-3 substituted indole derivatives found in natural products and exhibit different biological activities such as, indole-3-carbinol presents in vegetables like cabbage and broccoli, exhibits antiproliferative activity in many types of human cancer cells.[17,18] Indole barbitone derivatives such as 3-(2, 5-substituited-1H-indol-3yl)-1-phenyl prop-2-en-1-one exhibited significant antioxidant and DNA cleavage activities.[19] Very particularly, 3-aminoalkylated indole scaffolds are found to be present in numerous biologically potent natural products [20-21] and regarded as venerable pharmacophores in the on-going drug discovery processes [22-23]; natural products containing such indole moieties are reported to possess various pharmacological potentials.[24-28] Hence, such immense potential of indole nucleus as drug candidates has eventually

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motivated the synthetic chemists to explore different methods suitable for the synthesis of 3-substituted indoles.

Recent literatures suggest that several indole-3-substituted derivatives were synthesized using acid catalyzed Michael addition,[29] Mannich reaction,[30] multi component coupling reaction,[31] etc. Number of alkaloids, agrochemicals, pharmaceuticals and perfumes had been synthesized using several 3-substituited indoles as starting materials.

In the present work, we have developed indole-3-yl derivatives using Knoevenagel reaction, which get acetylated with simple acetyl chloride to give 1-acetyl-1H-indol-3-yl derivatives. All the synthesized compounds were characterized by ^{1}H-NMR, LCMS, FT-IR and UV-Visible spectroscopy.

2. Experiment

1H-NMR spectra were recorded on JEOL Eclipse and Eclipse plus spectrometers (^{1}H-NMR spectra recorded at 400 MHz) using either deuterated chloroform ($CDCl_3$) or hexadeuterated dimethylsulphoxide (DMSO-d6) as solvents. Chemical shifts (δ) are given in ppm vs. TMS (^{1}H-NMR) as an internal reference. Coupling constants are given in Hertz (Hz). ^{13}C-NMR spectra were recorded on Bruker spectrometers at 400 MHz using either deuterated chloroform ($CDCl_3$) as solvent. Spectra of LC-MS were recorded on LCQ ion Mass spectrometer. FT-IR spectra were measured on Agilent FT-IR spectrometer over the range of 400-4000 cm^{-1}. Absorption spectra were carried out on Shimadzu UV-1800 series. Melting points of all synthesized compounds were determined by open capillary tubes using Toshiba-melting point apparatus, expressed in ^oC.

Column chromatography was carried out by using silica gel 60-120 and 230–400 mesh. All the chemical reagents used for synthesis were purchased from Avra Synthesis^{TM}. Progress of the reaction was evaluated by Thin Layer Chromatography (TLC) by using petroleum ether and ethyl acetate as co-solvent mixture.

*2.1 General procedure for Synthesis of compounds (**2a-e**):*

To the round bottomed flask connected with dean stark apparatus contained a suspension of indole-3-carboxaldehyde (1 equiv) in toluene (15 v/w of starting material) was added active methylene compound (or nitromethane) (1.2 equiv) at room temperature followed by piperidine (0.05 equiv) and acetic acid (0.05 equiv), and heated to reflux for 6 h (monitored by TLC). Reaction mixture was cooled to room temperature and toluene was removed by rotavapor. To the crude compound was added water (4 v/w of starting material), resulted solid was filtered, washed with water, methanol and dried to yield compound-**2** as a solid. [32]

*2-((1H-indol-3-yl) methylene) malononitrile (**2a**):* Yield: 94%; M.p. 256-259 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 9.14 (s, 1H), 8.58 (d, *J*= 3.6 Hz, 1H), 8.12 (s, 1H), 7.76 (d, *J*= 8.4 Hz, 1H), 7.52 (d, *J*= 8.8 Hz, 1H), 7.42-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 150.5, 136.4, 131.0, 124.9, 123.4, 122.3, 118.1, 115.5, 115.2, 112.3, 110.4, 70.6; MS: *m/z*: 192 $[M-H]^-$; IR (ν/cm^{-1}): 3270 (N-H), 3020 (=C-H), 2217 (C≡N), 1344 (C-N); UV-Visible (nm): 386, 268, 213.

*3-(2-nitrovinyl)-1H-indole (**2b**):* Yield: 92%, M.p. 173-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.86 (brs, 1H), 8.30 (d, *J*= 13.2 Hz, 1H), 7.83-7.80 (m, 2H), 7.69 (m, 1H), 7.50-7.48 (m, 1H), 7.37-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 135.8, 135.0, 130.6, 130.2, 126.7, 126.5, 124.5, 119.4, 117.3, 114.2; MS: *m/z*: 187 $[M-H]^-$; IR (ν/cm^{-1}): 3390 (N-H), 3092 (=C-H), 1612 (-NO_2), 1240 (C-N); UV-Visible (nm): 393, 272, 218.

*Diethyl 2-((1H-indol-3-yl) methylene) malonate (**2c**):* Yield: 82%; M.p. 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.72 (s, 1H), 8.13 (s, 1H), 7.81-7.80 (m, 2H), 7.43 (m, 1H), 7 7.31-7.26 (m, 2H), 4.41-4.31 (m, 4H), 1.39-1.33(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.1, 165.4, 135.7, 135.0, 127.8, 127.4, 123.2, 121.4, 118.4, 111.7, 61.5, 61.2, 14.2, 14.0; MS: *m/z*: 288 $[M+H]^+$; IR (ν/cm^{-1}): 3256 (N-H), 2943 (=C-H), 1721 (C=O), 1241 (C-N), 1021 (C-O); UV-Visible (nm): 350, 263, 220.

*Dimethyl 2-((1H-indol-3-yl) methylene) malonate (**2d**):* Yield: 85%; M.p. 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.79 (s, 1H), 8.18 (s, 1H), 7.81-7.79 (m, 2H), 7.44-7.41 (m, 1H), 7.31-7.25 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 167.4, 164.0, 134.9, 132.8, 129.4, 127.6, 124.1, 123.8, 118.7, 115.5, 51.7, 51.0; MS: *m/z*: 260 $[M+H]^+$; IR (ν/cm^{-1}): 3319 (N-H), 2942 (=C-H), 1733 (C=0), 1226 (C-N); UV-Visible (nm): 350, 267, 218.

*Ethyl 3-(1H-indol-3-yl)-2-nitroacrylate (**2e**):* Yield: 80%; M.p. 65-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.88 (s, 1H), 7.97 (s, 1H), 7.78 (m, 2H), 7.47-7.45 (m, 1H), 7.35-7.29 (m, 2H), 4.40 (q, *J*=7.2 Hz, 2H), 1.39 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 169.4, 139.5, 134.8, 128.5, 126.9, 126.4, 123.9, 123.1, 118.3, 117.2, 111.0, 63.8, 14.2; MS: *m/z*: 259 $[M-H]^-$; IR (ν/cm^{-1}): 3258 (N-H), 1723 (C=0), 1624 (-NO_2), 1245 (C-N); UV-Visible (nm): 301, 263, 223.

*2.2 General procedure for Synthesis of compounds (**3a-e**):*

To the solution of compound-**2** (1 equiv.) in anhydrous DCM (20 v/w of starting material) was added triethyl amine (1.5 eq.) at room temperature under nitrogen atmosphere and cooled to 0 °C. Acetyl chloride (1.2 equiv) was added drop wise to the reaction mixture and left stirring at room temperature for 2 h. Reaction mixture was quenched with crushed-ice (20 w/w) and separated the biphasic layers. Aqueous layer was extracted with dichloromethane (20 v/w). Combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield compound-**3** as a solid. [33]

*2-((1-acetyl-1H-indol-3-yl) methylene) malononitrile (**3a**):* Yield: 92%; M.p. 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.74 (s, 1H), 8.52 (d, *J*= 8.2 Hz, 1H), 8.10 (s, 1H), 7.70 (d. *J*= 7.6 Hz, 1H), 7.55-7.46 (m, 2H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.4, 150.4, 135.8, 130.7, 125.1, 124.0, 122.8, 118.4, 116.0, 111.8, 110.8, 70.0, 24.2; MS: *m/z*: 192 $[M-CH_3CO]^-$; IR (ν/cm^{-1}): 3045 (=C-H), 2224 (C≡N), 1721 (C=0), 1214 (C-N); UV-Visible (nm): 384, 266, 213.

*1-(3-(2-nitrovinyl)-1H-indol-1-yl) ethanone (**3b**):* Yield: 94%; M.p. 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.52 (d, *J*= 8.0, 1H), 8.20 (d, *J*= 13.6 Hz, 1H), 7.93 (s, 1H), 7.84 (d, *J*= 13.6 Hz, 1H), 7.75 (d, *J*= 7.6 Hz, 1H), 7.52-7.43 (m, 2H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.2, 136.7, 136.4, 131.1, 131.0, 126.73, 126.70, 125.0, 120.0, 117.1, 114.0, 23.9; MS: m/z: 187 $[M-CH_3CO]^-$; IR (ν/cm^{-1}): 3045 (=C-H), 1729 (C=0), 1611 (-NO_2), 1206 (C-N); UV-Visible (nm): 365, 263, 232.

*Diethyl 2-((1-acetyl-1H-indol-3-yl) methylene) malonate (**3c**):*Yield: 93%; M.p. 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.45 (d, *J*= 8.4 Hz, 1H), 7.98 (m, 2H), 7.72 (d, *J*= 7.2 Hz, 1H), 7.45-7.36 (m, 2H), 4.39-4.32 (m, 4H), 2.67 (s, 3H), 1.39-1.33(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.4, 168.1, 165.2, 135.8, 135.2, 128.1, 127.3, 123.3, 121.7, 119.7, 117.7, 110.0, 109.8, 61.0, 60.6, 23.4, 14.4, 13.9; MS: *m/z*: 330 $[M+H]^+$; IR (ν/cm^{-1}): 2948 (=C-H), 1721 (C=O), 1210 (C-N); UV-Visible (nm): 333, 256, 228.

*Dimethyl 2-((1-acetyl-1H-indol-3-yl) methylene) malonate (**3d**):* Yield: 94%; M.p. 87-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 8.43 (d, *J*= 7.5 Hz, 1H), 7.98 (m, 2H), 7.70 (d, *J*= 6.7 Hz, 1H), 7.44-7.35 (m,

2H), 3.88 (s, 6H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.5, 167.2, 164.7, 135.4, 133.5, 129.4, 127.0, 126.2, 124.4, 124.3, 118.5, 116.7, 115.3, 52.7, 52.4, 23.8; MS: *m/z*: 302 $[M+H]^+$; IR (ν/cm^{-1}): 2951 (=C-H), 1723 (C=0), 1207 (C-N); UV-Visible (nm): 330, 257, 225.

*Ethyl 3-(1-acetyl-1H-indol-3-yl)-2-nitroacrylate (**3e**):* Yield: 90%; M.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.48 (d, *J*=7.9 Hz, 1H), 7.86(m, 2H), 7.72 (d, *J*=7.2 Hz, 1H), 7.49-7.41 (m, 2H), 4.44 (q, *J*=7.1 Hz, 2H), 2.70 (s, 3H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.5, 159.2, 139.4, 135.4, 128.7, 127.5, 126.6, 124.8, 124.0, 118.0, 117.0, 111.4, 63.0, 23.8, 14.1; MS: *m/z*: 259 $[M-CH_3CO]^-$; IR (ν/cm^{-1}): 2951 (=C-H), 1724(C=0), 1633 (-NO_2), 1224 (C-N); UV-Visible (nm): 301, 263, 223.

3. Result and discussion:

The target compounds were synthesized through the route as shown in the below scheme. The Knoevenagel condensation was used to synthesize the olefinic α-β unsaturated indole derivatives followed by acetylation with good yield and purity. Nitromethane, malononitrile, dimethyl malonate, diethyl malonate and ethyl nitro acetate were used to synthesis the various indole-3-substituited derivatives.

Nitromethane was observed faster compared to other reagents such as dimethyl malonate, diethyl malonate and ethyl nitro acetate, even its pKa value is 17.2 (in DMSO) which is higher than the dimethyl malonate (pKa-15.9, in DMSO), diethyl malonate (pKa-16.4, in DMSO) and ethyl nitro acetate (pKa-9.1, in DMSO). The reason could be the small in size and creates less steric hindrance during the formation of condensed product. The yield has found to be better with malonotrile followed by nitromethane, dimethyl malonate, diethyl malonate and ethyl nitroacetate (as shown in table), since the reaction time was extending and there was formation of impurities.

Acetylation was done by acetyl chloride and found to be much faster and more reactive than its carboxylic derivatives such as its anhydrides, acids, esters and amides. Piperidine base was used to expedite the acetylation.

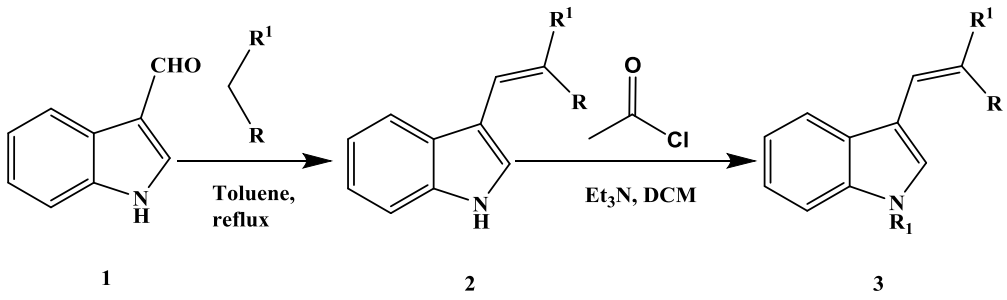

Figure 1. Synthetic route for 1-acetyl-1H-indol-3-yl derivatives

Table 1. Synthesis of indole-3yl (2a-e) and 1-acetyl-1H-indol-3-yl (3a-e) derivatives

Entry	R^1	R	R_1	Time (h)	% Yield
2a	CN	CN	H	4	94
2b	H	NO_2	H	7	92
2c	CO_2Et	CO_2Et	H	6	82
2d	CO_2Me	CO_2Me	H	6	85
2e	NO_2	CO_2Et	H	6	80
3a	CN	CN	MeCO	2	92
3b	H	NO_2	MeCO	1	94
3c	CO_2Et	CO_2Et	MeCO	2	93
3d	CO_2Me	CO_2Me	MeCO	2	94
3e	NO_2	CO_2Et	MeCO	2	90

4. Conclusion

In our studies, we have developed a simple and efficient method for the high-yielding synthesis of indole-3-yl derivatives via Knoevenagel reaction between indole-3-carboxaldehyde and nitromethane or active methylene compound in the presence of acetic acid and piperidine as a catalyst, which get acetylated from simple acetyl chloride and triethyl amine to give 1-acetyl-1H-indol-3-yl derivatives. Moreover, the protocol offers several other advantages such as simple experimentation with easy workup procedure, eco-friendly approach and better yields of obtained products.

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