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Synthesis and Characterization of Some Biologically Active Heterocycles Containing Nitrogen

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ABSTRACT

Indole derivatives such as compound 3c and 3d exhibited good antimycobacterial activity. We report here a concise procedure for prepration of novel 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2one.(3).This strategy would provide an efficient way to generate varied indole derivatives with pyrazol moiety for pronounced and promising anti mycobacterial activity.

Keywords: Double Salt, Aceto -Nitrile, Para-Toluene Sulphonyl Chloride.

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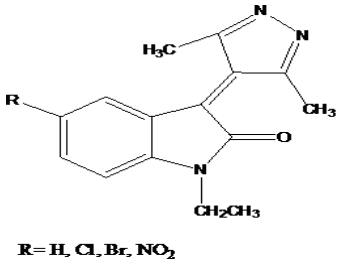
INTRODUCTION



R= H, Cl, Br, NO_2

The indole framework is a medicinally relevant scaffold and has become widely identified as a privileged structure. The indole nucleus is present in thousands of issolated natural products with diverse therapeutic activities, such as antiviral activities, antifungal activities, antimicrobial activities, antitumour activities and and recently antituberculosis activities. . So to met the emerging demands, many Laboratories and Industrial units are seeking new Anti –mycobacterial agents that could confer greater selectivity and lower toxicity [1,9,10]. Continuing our research for Anti-tubercular agents we have synthssized some derivatives of 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2one (3a-d) (IIIa-d) having pyrazol moiety[1,2,3]. These compounds were characterised by their spectral analysis (FT-IR, HI-NMR, MS).

MATERIALS AND METHODS

Drugs and Chemicals

Reactants for the synthesis of were procured from Sigma aldrich ltd. Media and other materials for antimicrobial activity were procured from Hi-media ltd. All the drugs and chemicals except the test compound (IIIa) were dissolved or diluted in distilled water and used for the experimentation purpose. **IIIa-d** was dissolved in 100% DMSO and dilutions were made with distilled water so that the final concentration of DMSO did not exceed (0.1 % v/v)

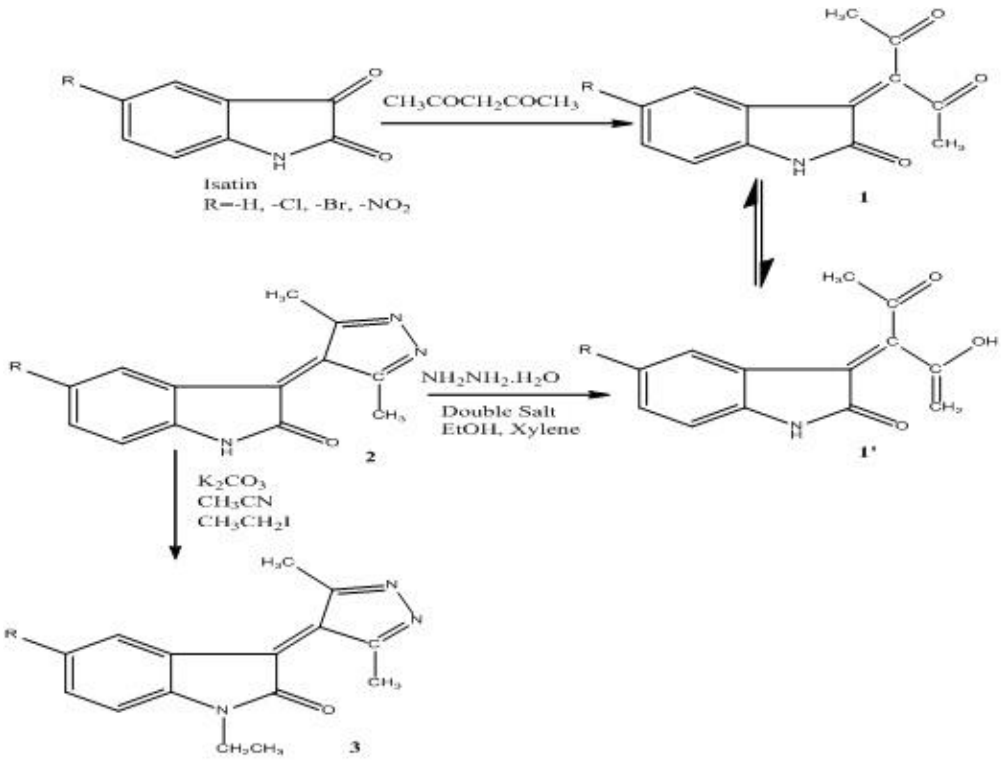
Experimental Melting points were determined using open capillary tube in Toshniwal Melting point apparatus and are presented without any correction. The infrared (IR) spectra were recorded on a FTIR-8310 Shimadzu spectrometer using potassium bromide pellets. The proton nuclear magnetic resonance (1H-NMR) specta were recorded on AMX 400 at 200 MHz using tetramethylsilane (TMS) as the internal standard and DMSO as solvent, collected from Central Instrumental Lab. Chandigarh University. All reagents were of the highest purity commercially available. The chemical shifts are expressed inpart per million (ppm) downfield from the internal standard; the coupling constants are in Hz, and signals are quoted as s(singlet), d(doublet), t (triplet), q (quartet), or m (multiplet). The purity of the compounds was checked by Thin Layer Chromatography using .Merck Pre-coated silica gel

Synthesis of Potassium Aluminium Sulphate Dodecahydrate

Add 25 ml of 3M KOH in a 250 ml beaker containingAluminium pieces. Proceed the reaction hood and filter it while hot to remove undissolved carbon particles. Cool the reaction mixture and acidify it with continuous stirring using 3M H2SO4. Concentrate the

mixture and allow it to stand for overnight to crystallize Potassium aluminium sulphate dodecahydrate, a catalyst(Double Salt) [2,4].

GF aluminium plates and Ethyl acetate : Chloroform (15:85) as solvent system.



Synthesis of 3-(2-oxo-1,2-dihydro-3H-Indole-3-ylidene) pentane-2,4-dione(1a)

Took 0.05mole of substituted isatin and 0.05 mole of acetyl-acetone in a conical flask. Mixture was subjected to cool in an ice bath, followed by addition of 1ml piperidine with continuous stirring. The reaction mixture was kept at freezing point temperaturefor 3 hours followed by addition of cold ethanol to break the lumps, filter the product and wash it with **3**

Ethanol cold, dried vaccum conditions.Mp:129 ^{0}C. Yield: 71%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,2943 Cm^{-1}, (C-H), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H); MS: m/z 228 (M^{+}, I= 67%), m/z 43 (I= 100%).

Synthesis of 5-Chloro- 3-(2-oxo-1,2-dihydro-3H-Indole-3-ylidene) pentane-2,4-dione(1b)

Mp:120 ^{0}C. Yield: 73%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,803 Cm^{-1} (C-Cl), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H); MS: m/z 228 (M^{+}, I= 67%), m/z 43 (I= 100%).

Synthesis of 5-Bromo- 3-(2-oxo-1,2-dihydro-3H-Indole-3-ylidene) pentane-2,4-dione(1c)

Mp:133^{0}C. Yield: 67%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,713 Cm^{-1} (C-Br), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H); MS: m/z 228 (M^+, I= 67%), m/z 43 (I= 100%).

Synthesis of 5-Nitro- 3-(2-oxo-1,2-dihydro-3H-Indole-3-ylidene) pentane-2,4-dione(1d)

Mp:109^{0}C. Yield: 63%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,721 Cm^{-1} (C-NO_2), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H); MS: m/z 228 (M^+, I= 67%), m/z 43 (I= 100%).

Synthesis of 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-Indol-2-one.(2a)[5]

0.05 moles of 1a-d and 0.06 moles of hydrazine were added in 40 ml of ethanol containing 500 mg of double salt with continuous stirring for 2 hours,followed by dilution with water. Extract the product with ethylacetate successively for three times. Decant it and passed it through sodium sulphate.Kept it under dessicator for drying.

.Mp:176 ^{0}C. Yield: 78%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,2949 Cm^{-1} (C-H), 1709 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H.), 1207 Cm^{-1}(C=N),1310 Cm^{-1}(N-N); MS: m/z 224 (M^+, I= 61%), m/z 15 (I= 100%).

Synthesis of 5-Chloro- 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-Indol-2-one.(2b)

Mp:183 ^{0}C. Yield: 58%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,803 Cm^{-1} (C-Cl), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H) 1207 Cm^{-1}(C=N),1310 Cm^{-1}(N-N); MS: m/z 224 (M^+, I= 61%), m/z 15 (I= 100%).

Synthesis of 5-Bromo- 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-Indol-2-one.(2c)

Mp:207^{0}C. Yield: 69%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,713 Cm^{-1} (C-Br), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H),1207 Cm^{-1}(C=N),1310 Cm^{-1}(N-N); MS: m/z 224 (M^+, I= 61%), m/z 15 (I= 100%). **4**

Synthesis of 5-Nitro- 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-Indol-2-one.(2d)

Mp:167^{0}C. Yield: 61%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH), IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,721 Cm^{-1} (C-NO_2), 1705 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H) 1207 Cm^{-1}(C=N), 1310 Cm^{-1}(N-N) MS: m/z 224 (M^+, I= 61%), m/z 15 (I= 100%).

Synthesis of 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2-one.(3a) [6,7]

A suspension of 2a-d(1.96 g, 6.0 mmol), 1.5 g k_2CO_3 and 0.97 ml methyl iodide(12mmol) in 30 ml acetonitrile was stirred at 68C for 2h.After the reaction mixture was cooled and filtered, the transparent yellow filtrate was evaporated in vaccum and then brown residue was recrystallized from ethyl acetate,obtaining the 3a-j as a pale coloured solid. .Mp:209 ^{0}C. Yield: 73%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH),i.9(t, 3H,MeH). IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,2949 Cm^{-1} (C-H), 1709 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H.), 1207 Cm^{-1}(C=N), 1310 Cm^{-1}(N-N),983 Cm^{-1}(C-N); MS: m/z 252 (M^+, I= 71%), m/z 29 (I= 100%).

Synthesis of 5-Chloro- 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2-one.(3b)

Mp:206^{0}C. Yield: 53%. ^{1}HNMR(200 MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH),i.9(t, 3H,MeH). IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,797 Cm^{-1} (C-Cl), 1709 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H.), 1207 Cm^{-1}(C=N), 1310 Cm^{-1}(N-N),983 Cm^{-1}(C-N); MS: m/z 252(M^+, I= 71%), m/z 29 (I= 100%).

Synthesis of 5-Bromo- 3-(3,5-dimethyl-4H-pyra1310zol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2-one.(3c)

Mp:223^{0}C.Yield: 64%. ^{1}HNMR(200MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH),i.9(t, 3H,MeH). IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,717 Cm^{-1} (C-Br),1709 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H.), 1207 Cm^{-1}(C=N), 1310 Cm^{-1}(N-N),983 Cm-1 (C-N); MS: m/z 252(M^+, I= 71%), m/z 29 (I= 100%).

Synthesis of 5-Nitro- 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2-one.(3d)

Mp:I83^{0}C.Yield: 61%. ^{1}HNMR(200MHz,TMS):δ 7.4(s, 3H, $H_{Ar)}$,4.1(s, 1H, NH) 2.3(s, 3H, MeH),i.9(t, 3H,MeH). IR(KBr) Cm^{-1} :1453 Cm^{-1}(C-C st), 1571Cm^{-1}(C=C) ,713 Cm^{-1} (C-NO_2), 1709 Cm^{-1}(C=O), 3267 Cm^{-1}(N-H.), 1207 Cm^{-1}(C=N), 1310 Cm^{-1}(N-N),983 Cm^{-1}(C-N); MS: m/z 252(M^+, I= 71%), m/z 29 (I= 100%).

RESULTS AND DISCUSSION

The synthetic pathway followed in the prepration of the compounds is outlined in the scheme. Pentane-2,4-dione(1) was obtained by reacting 5-substituted Isatin with acetyl acetone in presence of piperidine.It undergoes tautomerizes to compound(1'). ompound(1) was treated treated with Hydrazine in presence of Double Salt acting as catalyst with continuous stirring for 2-3hrs to afford 3-(3,5dimethy4H-pyrazol-4-ylidene)-1,3-dihydro-2H-Indol-2-one.(2)Compound(2)was Nalkylated with ethyl iodide in acetonitrile to give 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2one.(3). The IR spectrum of 1 displayed strong bands at 3267 cm^{-1} and 1705 cm^{-1} respectively due to N-H and C=O stretching. The C-H stretching in 1 was observed at 3025 cm^{-1} while in case of **5.**

2 a strong peak was observed at 2910cm^{-1} due to C-CH_3 stretching supporting the formation of compound(2). A peak was observed at 3543 cm^{-1} because of O-H stretching supporting tautomerization.Peak observed at 1310 is due to N-N stretching.In the ^{1}HNMR of 1-3 a singlet due to NH is observed at 7.4. Also a singlet is observed at 2.3 due to 3H of CH_3 group. At 7.3-7.5 a singlet is observed due to 3H of aromatic ring($H_{Ar)}$.

CONCLUSION

So we have concluded that Double Salt i.e $KAl(SO_4)_2.12H_2O$ can be a better catalyst because it is non-toxic, inexpensive, re-usable and easily available for the synthesis of 3-(3,5-dimethyl-4H-pyrazol-4-ylidene)-1-ethyl-1,3-dihydro-2H-Indol-2one.(3).

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