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ABSTRACT

In this paper we are discussing about conversion of indole aldehydes to N-substituted Indole aldehydes and followed by reversibly reproduction of indole aldehydes from substituted indoles by using bases. N-substituted Indole aldehydes are medicinally patents and widely used to cure diseases. The synthesis started with indole-3-aldehyde. In the beginning compound was prepared in situ using Henry reaction of aldehyde with nitro methane in presence of ammonium acetate as a base. Thus, N-benzene sulphonyl protected aldehyde was synthesized from aldehyde using benzene sulphonyl chloride in presence of KOH as a base in DMSO. Now aldehyde was reacted with diamine in methanol at reflux condition deprotection of -N-SO2Ph has taken place instead of cyclization. . The benzyl protected aldehyde was synthesized by using benzyl bromide, NaH in DMF.

Keywords: Indoles, Henry reaction, benzyl bromide, cyclization.

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CHEMISTRY RESEARCH ARTICLE

Synthesis of some novel biologically potent N-substituted Indole aldehydes from indolealdehyde by Henry reaction

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ABSTRACT

In this paper we are discussing about conversion of indole aldehydes to N-substituted Indole aldehydes and followed by reversibly reproduction of indole aldehydes from substituted indoles by using bases. N-substituted Indole aldehydes are medicinally potents and widely used to cure diseases. The synthesis started with indole-3-aldehyde. In the beginning compound was prepared in situ using Henry reaction of aldehyde with nitro methane in presence of ammonium acetate as a base. Thus, N-benzene sulphonyl protected aldehyde was synthesized from aldehyde using benzene sulphonyl chloride in presence of KOH as a base in DMSO. Now aldehyde was reacted with diamine in methanol at reflux condition deprotection of -N-SO2Ph has taken place instead of cyclization. . The benzyl protected aldehyde was synthesized by using benzyl bromide, NaH in DMF.

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1. INTRODUCTION

The bis-indole alkaloids, nortopsentins A-D (Figure 1, **1-4**) displayed[1-4] cytotoxic activity against P-388 cells with IC_{50} values of 7.6, 7.8, 1.7 and 0.9 µg/mL respectively. The bisindole alkaloid, topsentin (**5**) inhibited[5] the proliferation of cultured human and murine tumor cells. It exhibited in vitro activity against P-388 with IC_{50} 3 µg/mL and human tumor cell with IC_{50} 20 µg/mL. Deoxytopsentin (**6**) showed[6] the antiproliferative activity against human bronocopulmanary cancer cells with IC_{50} 6.3 µg/mL. It also showed moderate activity against breast cancer and hepatoma with IC_{50} 10.7 and 3.3 µg/mL respectively. Dragmacidin (**7**) showed[7] in vitro cytotoxicity with IC_{50} 15 µg/mL against P-388 cell lines and 1-10 µg/mL against A-549 (human lung), HCT-8 (human colon) and MDAMB (human mammary) cancer cell lines.

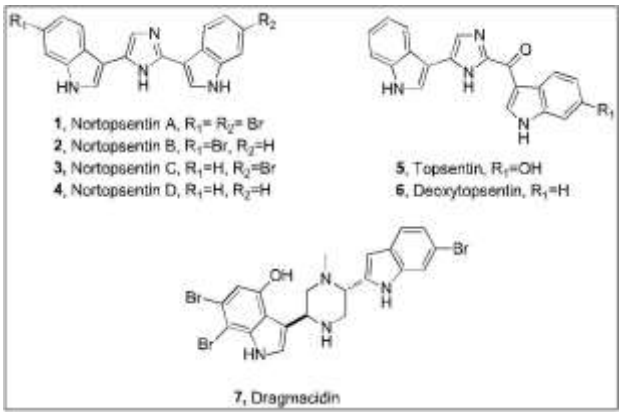


Figure 1

Hyrtinadine A (**8**) is a novel bis-indole alkaloid having 2, 5-disubstituted pyrimidine skeleton. It was isolated[8] from an Okinawan marine sponge of the Hyrtios genus. This compound exhibited in vitro cytotoxic activity against murine leukemia L1210 cells with IC_{50} 1 µg/mL and human epidermoid carcinoma KB cells with IC_{50} 3 µg/mL.

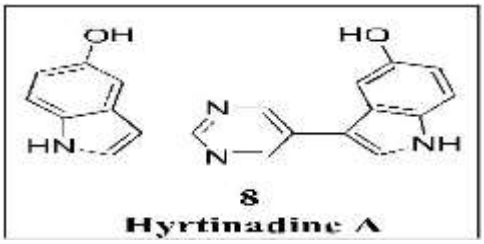
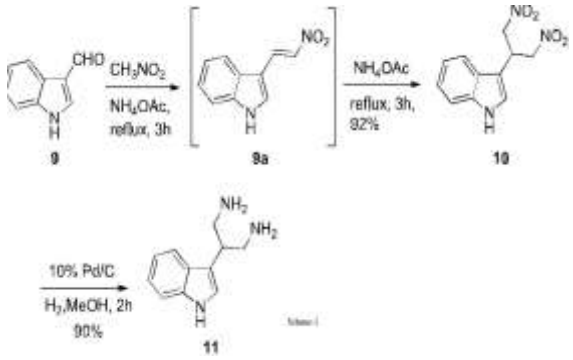


Figure 2

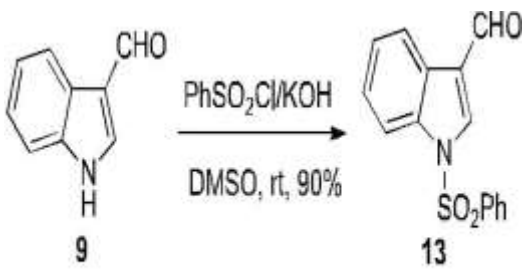
2. RESULTS AND DISCUSSION

In the beginning, it was planned to carry out a pilot synthetic scheme, starting with an unsubstituted indole-3-aldehyde to produce an analogue of hyrtinadine A and subsequently, it could be implemented for the target molecule **8**. According to the retro synthetic scheme, the synthesis started with indole-3-aldehyde **9** (Scheme1). In the beginning compound **9a** was prepared in situ using Henry reaction of aldehyde **9** with nitro methane in presence of ammonium acetate as a base. Further, confirming the formation of new product on TLC, without isolating product **9a**, some more ammonium acetate was added to the reaction mixture. After refluxing the reaction mixture for 2 hours, the reaction was worked up to get a solid. Column chromatographic separation furnished a pale yellow solid in 95% yield, having M. p. 95 °C which was characterized by analytical and spectral data. From this data structure **10** was assigned to this product. In HRMS it showed molecular ion peak at 272.0642 for $C_{11}H_{11}N_3NaO_4$ (M+Na). ^{1}H NMR showed multiplates at δ 4.56 for one proton, at δ 4.99-5.03 and δ 5.09-5.13 for protons of two methylene group. Five aromatic protons were resonating between δ 7.02-7.69. A broad singlet at δ 11.15 for NH proton was also seen. ^{13}C NMR displayed singlets at δ 33.88 and 77.09 for methine and methylene carbons respectively and remaining eight carbons were resonating at appropriate positions. All the data was consistent with the structure **10** and with the reported[11] values. The formation of product **10** can be explained as the initial formation of nitro styrene **9a** in the Henry reaction and further Michael addition of nitro methane on nitro styrene **9a**. We have modified the reported method[11] by using different base and nitro methane itself as a solvent. The yield in the modified method was shown to be very good (92%) as compared to the reported method (55%).a

The reduction of dinitro compound **10** using 10% Pd/C in methanol yielded diamine **11**. This diamine was characterized immediately after work up due to its instability and used for further reaction without purification. The NMR of diamine **11** was taken in deuterated methanol due to its poor solubility in usual solvents. ^{1}H NMR (Figure 4) showed a doublet for four protons of two methylene groups at δ 2.74-2.76 with J = 6.4 Hz, multiplate for one methine proton at δ 2.79-2.86 and five aromatic protons between δ 6.91-7.49. ^{13}C NMR exhibited singlets at 44.36 and 44.91 for aliphatic carbons and eight singlets in aromatic region. All NMR data was consistent with the reported[11] values.

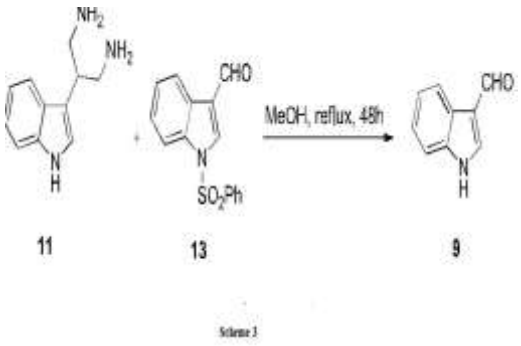


We thought to use protected indole-3-aldehyde instead of indole-3-aldehyde (**9**). Thus, N-benzene sulphonyl protected aldehyde **13** was synthesized from aldehyde **9** using benzene sulphonyl chloride in presence of KOH as a base in DMSO (Scheme 2). The ^{1}H NMR (Figure 6) showed singlet for aldehyde group at δ 10.10 and ten signals for protons in aromatic region. ^{13}C NMR displayed aldehydic carbon at δ 185.31 and twelve singlets for remaining carbons at appropriate positions. The spectral data was consistent with reported[12] values.

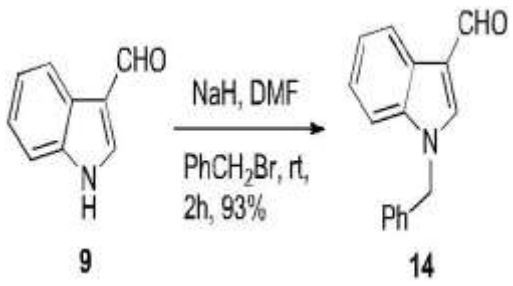


Scheme 2

Now, aldehyde **13** was reacted with diamine **11** in methanol at reflux condition (Scheme 3). The reaction was monitored by TLC, a newly formed compound was purified by column chromatography to get a solid product. 1H NMR spectrum showed a quintet for two protons at δ 7.24 with J = 7.27 Hz, two doublets at δ 7.50-7.53 with J = 8.11 Hz and at δ 8.08-8.11 with J = 7.15 Hz for one proton each, two singlets at δ 8.29 and δ 9.94 for one proton each and broad singlet at δ 12.14 for one proton. ^{13}C NMR displayed a singlet at δ 185.40 and eight singlets between112.85-138.89. From the spectral data, the compound confirmed as indole-3-aldehyde (**9**). From this observation, it was found that the deprotection of -N-SO_2Ph has taken place instead of cyclization.



Benzyl protection was selected as it is removed under hydrogenation conditions. The benzyl protected aldehyde **14** was synthesized in 93%, using benzyl bromide, NaH [14-20] in DMF (Scheme 4). ^{1}H NMR showed a singlet for methylene protons at δ 5.36, a singlet at δ 10.00 for aldehydic proton and ten signals for remaining protons in aromatic region. ^{13}C NMR (Figure 9) showed singlet at δ 50.29 for methylene carbon, singlet at δ 185.20 for aldehyde carbonyl group and twelve singlets for remaining aromatic carbons. The spectral data was consistent with reported[13] values.



Scheme 4

3. CONCLUSION

The various attempts towards the synthesis of analogue of Hyrtinadine A were performed. Further conformed by spectral analysis.

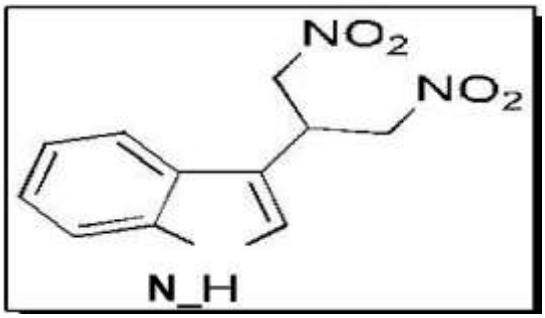
ACKNOWLEDGEMENTS

Authors are thankful to the director IICT – Hyderabad for providing NMR, ^{13}CNMR, MS data.

Experimental Section

3-(1, 3-dinitropropan-2-yl)-1H-indole (10)

To a suspension of aldehyde **9** (1g, 6.89 mmol) in Nitro methane (25 mL) was added ammonium acetate (0.98 g, 10.3 mmol). The mixture was refluxed for 3 h. The formation of nitrystyrene was visualized on TLC. After total conversion of aldehyde **9** into nitrystyrene on TLC, ammonium acetate (0.98 g, 10.3 mmol) was added and reaction mixture was refluxed for further 3 h. Then reaction mixture was concentrated, water (50 mL) was added to the residue and extracted with CH_2Cl_2 (3x20 mL). The organic layers were separated, washed with brine and dried over Na_2SO_4. After concentration, the crude product was purified by column chromatography (pet ether: ethyl acetate) to give Michael adduct (**10**) as pale yellow solid (1.57 g, 92%). M. p. 98 °C.



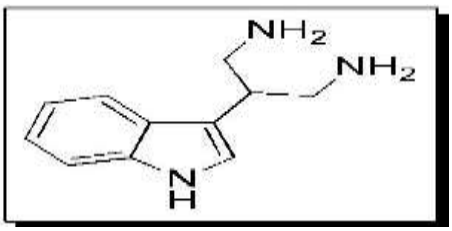
^{1}H NMR (500 MHz, DMSO-d_6): ⊚ 4.51-4.59 (m, 1H), 4.98-5.04 (m, 2H), 5.08-5.14 (m, 2H), 7.04 (ddd, J = 7.93, 7.02, 0.92 Hz, 1H), 7.12 (td, J = 7.55, 1.07 Hz, 1H), 7.33-7.43 (m, 2H), 7.67-7.69 (d, J = 7.93 Hz, 1H), 11.15 (brs., 1H).

^{13}C NMR (125 MHz, DMSO-d_6): ⊚ 33.88, 77.09, 108.56, 111.78, 118.17, 119.06, 121.54, 123.87, 125.74, 136.11.

HRMS (ESI): m/z calcd for $C_{11}H_{11}N_3NaO_4$ $(M+Na)^+$, 272.0642; found, 272.0642.

2-(1H-indol-3-yl) propane-1, 3-diamine (11)

In a 100 mL round-bottom flask, the dinitro compound (**10**) (1.00 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (0.20 mmol) was added (carefully), to which a H_2 balloon was connected. The resulting suspension was stirred at room temperature for 4 h (TLC) and the mixture filtered through Celite and washed with MeOH (5 mL). The solvent was evaporated under reduced pressure to afford the diamine **11**, which was used further without further purification.

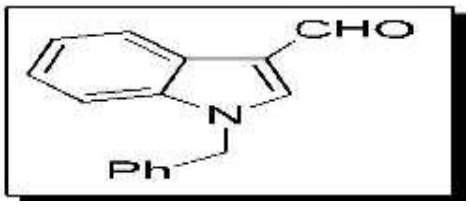


^{1}H NMR (300 MHz, Methanol-d_4): δ 2.74-2.76 (d, J = 6 Hz, 4H), 2.79-2.86 (m, 1H), 6.90-6.97 (m, 1H), 7.00-7.06 (m, 2H), 7.36 (d, J = 8.21 Hz, 1H), 7.46-7.49 (d, J = 7.62 Hz, 1H).

^{13}C NMR (75 MHz, Methanol-d_4): δ 44.36, 44.91, 112.89, 114.84, 119.95, 120.06, 122.85, 124.15, 128.06, 138.34.

1-benzyl-1H-indole-3-carbaldehyde (14)

To a stirred solution of aldehyde **9** (1 g, 3.44 mmol) in dry DMF (15 ml) at 0°C was added NaH (60% dispersion in mineral oil, 0.330 g, 8.6 mmol). The mixture was stirred for 30 min at 0 °C and allowed to warm to 10 °C. Then benzyl bromide (0.409 mL, 3.44 mmol) was added and the mixture was stirred for 2 h. It was added water (25 mL). The solid was precipitated out, which was filtered, washed with water, dried which gave product **14**. M.p. 107 °C



^{1}H NMR (500 MHz, DMSO-d_6): ⊚ 5.54 (s, 2H), 7.22-7.35 (m, 7H), 7.55-7.62 (m,

1H), 8.09-8.17 (m, 1H), 8.47 (s, 1H), 9.95 (s, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): ⊚⊚49.82, 111.41, 117.42, 121.11, 122.58, 123.64, 124.83, 127.35, 127.80, 128.73, 136.77, 136.98, 141.01, 184.72.

Procedure for the reaction of diamine 11 and aldehyde 9

Diamine (**11**, 1 equivalent) was dissolved in (15 mL) methanol/ethanol/t-BuOH. The solution of indole-3-aldehyde (**9**, 1.2 equivalent) in the same solvent was added to the above solution at various temperatures (0 °C, rt) and heated to reflux. The reaction was monitored by TLC and continued up to 48 hours, and then solvent was removed under vacuum. The ethyl acetate (10 mLx2) was added to the residue to remove alcohol and residual water from the crude mixture. The residue was chromatographic on silica gel. The reactions using aldehydes **13**, **14, 21** were also carried out in similar fashion, wherever needed the catalysts and microwave conditions were used.

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