Original Research Paper

Volume-9 | Issue-6 | June-2019 | PRINT ISSN No. 2249 - 555X

Chemistry

SYNTHESIS OF PYRAZOLYL BIS INDOLYL METHANE AND ITS DERIVATIVES USING NOVEL CLAY CATALYST

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ABSTRACT The present paper gives the application of Novel Clay material obtained from Bashir farm Jatadevale, Tq Pathardi; Dist. Ahmednagar for the synthesis bis indolyl methane derivatives from 1, 3-diphenyl-1-H-pyrazole-4-carboxaldehyde was reacted with indole to form a new species of biologically active moiety to gives very clean and good product. Additionally keeping the view of biological and medicinal properties of pyrazoles and the potential chemistry of indole hence the chemistry of both moieties are synthesized by condensation of these two in search of designing biological active compounds that could aggressively work against bacterial species and cancer cell.

KEYWORDS : Novel Clay, EDS, FESEM, XRD, bis (indolyl) methane, 1, 3-diphenyl-1H-pyrazole-4-carboxaldehyde, Nanomaterial.

1. INTRODUCTION

Cancer is a major health problem globally, considered the second leading cause of death after the heart disease. Among the various types of malignant tumors, breast cancer causes the second leading deaths in women [1]. The bis (indolyl) methane exhibit a wide range of biological activity against various tumor cells. Developing new species with wide range of pharmacological activity and also low cytotoxicity represents a very important aspect in the biochemical research area. Recently it has been considerable amount of progress in 1, 3-diarylpyrazole chemistry because of the recognition of importance of the pyrazole structure in biological processes as antimicrobial, anti-inflammatory, antitubercular, antitumor, anti-angiogenesis, antiparasitic, antiviral and also possesses analgesic and anxiolytic activity [2]. Indole and its derivatives have wide range of applications in biological and medicinal activities [3]. Bis-indole derivatives not only increase the natural metabolism of hormones in the body but also used as anticancer drug [4]. Bis-indole derivatives act as antifungal activity [5]. Bis (indolyl) methane are members of promising new drug class these are diarylamidine derivatives that target DNA synthesis, providing a broad spectrum antibacterial activity [6]. For the synthesis of bisindole from indole different catalyst were reported such as Ln (OTf)$_3$, I$_2$, PCl$_5$, PPA/SiO$_2$, silica sulphuric acid, Lewis acid, protic acid [7]. However many of procedures have significant limitation such as required stoichiometric amount of catalyst, long reaction time, expensive catalyst, low yield and use of environmentally toxic reagents. In the present work clay is of low cost and overcome some of these limitations. Keeping the view biological and medicinal properties of pyrazoles and the potential chemistry of indole we condense both moieties in search of designing biological active compounds that could aggressively work against resistant bacterial species and cancer cell. For this accomplishment 1, 3-diphenyl-1H-pyrazole-4-caboxaldehyde was reacted with indole to form a new species of biologically active moiety.

2. Experimental Protocols.

2.1. Chemistry.

All chemicals were purchased from major chemical suppliers of good quality and used without further purification. As a part of our study, Bis-indole derivatives were synthesized using Novel Clay catalyst. Reactions were monitored by TLC techniques. FT-IR was recorded in KBr, H NMR of synthesized compounds, X-Ray Powder diffraction (XRD), energy-dispersive X-Ray Spectroscopy (EDS) and Field Emission Scanning Electron Microscope (FESEM) by using instrument Nova Nano SEM 450 UOP were recorded from Savitribai Phule Pune University, Pune, INDIA

2.2. Activation of catalyst.

The activation of clay catalyst was done as per the procedure explained in our previous report [3, 6 and 8]. The clay was obtained from the field of Bashir Farm (Jatadevale) Tq Pathardi & Dist. Ahmednagar. Initially, the clay was crushed in a fine powder in mortar, washed with distilled water and soaked in (0.1 M) H_2SO_4 for 24 hour. Later, it was filtered and was washed by plenty of distilled water to remove acidity, it was then dried it at 110°C. After cooling and characterization (XRD, EDS and FESEM) the clay was ready for use in reactions.

2.3. General procedure for Synthesis of Synthesis of 1, 3-diphenyl-1-H-pyrazole-4-carbaldehyde.

2.3.1. Preparation of Hydrazone derivatives of acetophenone.

(1 mole) of acetophenone and (1 mole) of phenyl hydrazine beaker add (2 to 3) drop of acetic acid in mixture stir well and heat reaction mixture in water bath for five minutes solid hydrazone product is separated recrystallized with ethanol.

2.3.2. Conversion of hydrazone to Carboxaldehyde.

Take (45 ml) DMF in R.B. Flask and cool it at 0°C in ice bath add it (20 ml) $POCl_3$ drop wise to maintain temperature below 10°C dissolve hydrazone prepared in last stage to minimum amount of DMF in beaker add this mixture to round bottom Flask drop by drop to maintain temperature below 20°C after complete of addition stir well and keep the reaction mixture at room temperature for 30 minute then pour this reaction mixture into ice cold water filter the product recrystallize with ethanol.

2.4. Synthesis of bis (indolyl) methane derivatives.

The mixture of (1 mole) of aldehyde, (2 mole) of indole and (0.10 mg) of catalyst in ethyl acetate in conical flask with magnetic needle and stirthis reaction mixture well on magnetic stirrer for specific period. The reaction was monitored by TLC.Reactions checked by TLC then add 10ml dichloromethane then reaction mixture was filtered. Catalyst is separated by filtration and reused. Then some amount of N-hexane is added in solvent. This mixture was kept in deep freezer pure crystals are separated. As a part of our study of the chemistry indole [biological active moiety] we have synthesized 3-((1H-indol-3-yl)(1,3-diphenyl-1H-pyrazol-4-yl)methyl)-1H-indole and it's derivatives by using novel Clay catalyst. [Scheme]

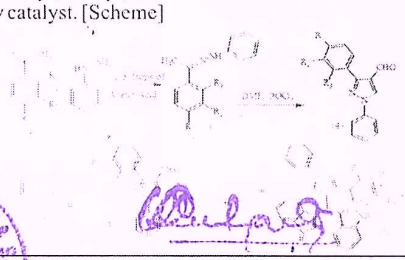

Table 1. The indole and aldehydes along with product is gives true yield. The reaction completes from 2 to 5 hours with quite good yield 74 to 83 %. The catalyst is characterized using EDS, FESEM and X-ray Diffraction.

Sr. No.	R_1	R_2	R_3	Yield (%)
7a	H	H	H	80
7b	NH_2	H	H	81
7c	Br	H	H	78
7d	OCH_3	H	H	76
7e	H	H	NH_2	76
7f	H	H	Br	78
7g	H	H	OCH_3	77
7h	H	NH_2	H	82
7i	H	Br	H	77
7j	H	OCH_3	H	74

3.1. RESULT AND DISCUSSION:

The indole and substituted 1, 3-diphenyl-1H-pyrazole-4-caboxaldehyde along with Novel Clay catalyst gives good product yield [table 1] the reaction completes from 2 to 5 hours, the spectral data of final product (7a to 7j) is given below.

3.1.1. 7a) ***3-((1H-indol-3-yl)(1,3-diphenyl-1H-pyrazol-4-yl)methyl)-1H-indole.*** Yield 80%; IR spectrum, cm^{-1}: 3623, 3411, 3123, 3016, 2820, 2850, 1615, 1340, 1089, 733 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 6.8(s,1H), 7.0(dd,1H, Ar-H),7.2(m,1H, Ar-H), 7.3(m, 2H), 7.4(m, 3H), 7.5(m,2H), 7.6(dd, 3H), 7.8(dd, 2H), 7.9(dd, 2H), 8.0(dd, 2H), 8.1(s, 1H), 9.3(s, 2H,), 9.9(bs, 2H, pyrrole ring N-H); ES-MS *m/z* 464 [M+]; 463, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{32}H_{25}N_3$ (464.2): C, 82.73; H, 5.21; N, 12.06; Found C, 82.14; H, 5.30; N, 12.33

3.1.2. 7b) ***4-(4-(di(1H-indol-3-yl)methyl)-1-phenyl-1H-pyrazol-3-yl)benzenamine.*** Yield 81%; IR spectrum, cm^{-1}: 3419, 3213, 3113, 3019, 2922, 2849, 1615, 1339, 1078, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.2 (s, 2H, Ar-NH), 6.8 (dd,2H), 7.2(m, 3H, Ar-H), 7.4(m, 2H), 7.5(m, 4H), 7.6(m, 3H), 7.8(dd, 2H), 7.94(dd, 2H), 8.1(dd, 1H), 8.3(dd, 1H), 8.8(s, 1H), 9.8(bs, 1H, pyrrole ring N-H), 9.9(bs, 1H, pyrrole ring N-H); ES-MS *m/z* : 479 [M+]; 356, 355, 354, 240, 241, 116; Anal. Calcd. For $C_{33}H_{25}N_5$ (479.2): C, 80.14; H, 5.25; N, 14.60; Found C, 80.14; H, 5.30; N, 11.33

3.1.3. 7c) ***3-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole.*** Yield 78%; IR spectrum, cm^{-1}: 3529, 3413, 3113, 3019, 2922, 2849, 1615, 1339, 1078, 731, 678, 540. cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.1(dd, 2H), 7.4(m, 2H), 7.5(m, 2H), 7.6(m, 4H), 7.7(m, 3H, Ar-H), 7.8(dd, 2H, Ar-H), 7.94(dd, 2H), 8.1(dd, 2H), 8.4(dd, 1H), 9.1(s, 1H), 10.1(s, 2H, pyrrole ring N-H); ES-MS *m/z*: 544 [M+2]; 542,543, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{32}H_{22}BrN_3$ (542.1): C, 70.72; H, 4.27; Br, 14.70; N, 10.31; Found C, 80.14; H, 5.30; N, 11.33

3.1.4. 7d) ***3-((1H-indol-3-yl)(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-indole.*** Yield 76%; IR spectrum, cm^{-1}: 3425, 3200, 3113, 3019, 1599, 1499, 1150, 1084, 732; cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 3.82 (s, 3H, ArOC<u>H</u>$_3$), 6.9(dd, 2H), 7.2(m, 2H), 7.3(m, 3H), 7.5(m, 4H), 7.6(m, 3H), 7.8(dd, 2H), 7.94(dd, 2H), 8.1(dd, 1H), 8.4(dd, 1H), 8.6(S, 1H), 9.9(s, 1H, pyrrole ring N-H), 10.1(s, 1H, pyrrole ring N-H); ES-MS *m/z*: 495 [M+1]; 494, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{33}H_{26}N_4O$ (494.2): C, 80.14; H, 5.30; N, 11.33; Found C, 80.14; H, 5.30; N, 11.33

3.1.6. 7e) ***2-(4-(di(1H-indol-3-yl)methyl)-1-phenyl-1H-pyrazol-3-yl)benzenamine.*** Yield 76%; IR spectrum, cm^{-1}: 3409, 3211, 3103, 3013, 2912, 2839, 1611, 1319, 1074, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.4 (s, 2H, Ar-NH$_2$), 6.7 (dd,2H), 7.1(m, 3H, Ar-H), 7.3(m, 2H), 7.4(m, 4H), 7.6(m, 3H), 7.7(dd, 2H), 7.84(dd, 2H), 8.1(dd, 1H), 8.3(dd, 1H), 8.9(s, 1H), 9.7(bs, 1H, pyrrole ring N-H), 9.8(bs, 1H, pyrrole ring N-H); ES-MS *m/z* : 479 [M+]; 356, 355, 354, 240, 241, 116; Anal. Calcd. For $C_{33}H_{25}N_5$ (479.2): C, 80.14; H, 5.25; N, 14.60; Found C, 80.14; H, 5.30; N, 11.33

3.1.7. 7f) **3-((3-(2-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole.** Yield 78%; IR spectrum, cm^{-1}: 3523, 3411, 3103, 3012, 2912, 2839, 1613, 1334, 1068, 729, 677, 544. cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.2(dd, 2H), 7.3(m, 2H), 7.5(m, 2H), 7.6(m, 4H), 7.7(m, 3H, Ar-H), 7.8(dd, 2H, Ar-H), 7.984(dd, 2H), 8.1(dd, 2H), 8.4(dd, 1H), 8.8(s, 1H), 10.1(s, 2H, pyrrole ring N-H); ES-MS *m/z*: 544 [M+2]; 542,543, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{32}H_{22}BrN_3$, (542.1): C, 70.72; H, 4.27; Br, 14.70; N, 10.31; Found C, 80.14; H, 5.30; N, 11.33

3.1.8. 7g) ***3-((1H-indol-3-yl)(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-indole.*** Yield 77%; IR spectrum, cm^{-1}; 3413, 3197, 3109, 3029, 1589, 1499, 1151, 1083, 731; cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 3.92 (s, 3H, ArOC<u>H</u>$_3$), 6.9(dd, 2H), 7.2(m, 2H), 7.4(m, 3H), 7.5(m, 4H), 7.6(m, 3H), 7.7(dd, 2H), 7.84(dd, 2H), 8.2(dd, 1H), 8.4(dd, 1H), 8.5(S, 1H), 9.8(s, 1H, pyrrole ring N-H), 10.1(s, 1H, pyrrole ring N-H); ES-MS *m/z*: 495 [M+1]; 494, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{33}H_{26}N_4O$, (494.2): C, 80.14; H, 5.30; N, 11.33; Found C, 80.14; H, 5.30; N, 11.33

3.1.10. 7h) ***3-(4-(di(1H-indol-3-yl)methyl)-1-phenyl-1H-pyrazol-3-yl)benzenamine.*** Yield 82%; IR spectrum, cm^{-1}: 3425, 3203, 3111, 3017, 2920, 2848, 1616, 1333, 1068, 739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.0 (s, 2H, Ar-NH$_2$), 6.6 (dd,2H), 7.0(m, 3H, Ar-H), 7.2(m, 2H), 7.3(m, 4H), 7.4(m, 3H), 7.6(dd, 2H), 7.74(dd, 2H), 8.2(dd, 1H), 8.3(dd, 1H), 8.7(s, 1H), 9.8(bs, 1H, pyrrole ring N-H), 9.9(bs, 1H, pyrrole ring N-H); ES-MS *m/z* : 479 [M+]; 356, 355, 354, 240, 241, 116; Anal. Calcd. For $C_{33}H_{25}N_5$, (479.2): C, 80.14; H, 5.25; N, 14.60; Found C, 80.14; H, 5.30; N, 11.33

3.1.11. 7i) ***3-((3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole.*** Yield 77%; IR spectrum, cm^{-1}: 3522, 3412, 3103, 3017, 2919, 2852, 1619, 1344, 1081, 741, 683, 540. cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.2(dd, 2H), 7.5(m, 2H), 7.6(m, 2H), 7.7(m, 4H), 7.8(m, 3H, Ar-H), 7.9(dd, 2H, Ar-H), 7.98(dd, 2H), 8.3(dd, 2H), 8.6(dd, 1H), 9.2(s, 1H), 10.2(s, 2H, pyrrole ring N-H); ES-MS *m/z*: 544 [M+2]; 542,543, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{32}H_{22}BrN_3$, (542.1): C, 70.72; H, 4.27; Br, 14.70; N, 10.31; Found C, 80.14; H, 5.30; N, 11.33

3.1.12. 7j) ***3-((1H-indol-3-yl)(3-(3-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-indole.*** Yield 74%; IR spectrum, cm^{-1}; 3433, 3198, 3109, 3024, 1598, 1499, 1149, 1086, 728; cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 3.80 (s, 3H, ArOC<u>H</u>$_3$), 6.7(dd, 2H), 7.0(m, 2H), 7.1(m, 3H), 7.3(m, 4H), 7.4(m, 3H), 7.6(dd, 2H), 7.84(dd, 2H), 8.0(dd, 1H), 8.2(dd, 1H), 8.3(S, 1H), 9.7(s, 1H, pyrrole ring N-H), 9.9(s, 1H, pyrrole ring N-H); ES-MS *m/z*: 495 [M+1]; 494, 368, 367, 366, 350, 252, 251, 116; Anal. Calcd. For $C_{33}H_{26}N_4O$, (494.2): C, 80.14; H, 5.30; N, 11.33; Found C, 80.14; H, 5.30; N, 11.33

3.2. Catalytic activity.

The activated catalyst gives good yield for three times. When 1, 3-diphenyl-1H-pyrazole-4-carbaldehyde reacts with indole in presence of clay as a catalystin ethyl acetate as solvent, 3-((1H-indol-3-yl)(1,3-diphenyl-1H-pyrazol-4-yl)methyl)-1H-indole was obtained in good yield. This is ecofriendly catalyst that's why it is easily separated and use as catalyst in same reaction we used this catalyst in same reaction scheme in several times we get better yield and better catalytic activity but as number of cycle increases more than four cycle yield is poor percent of yield and number of cycles of reaction given in fig 1.

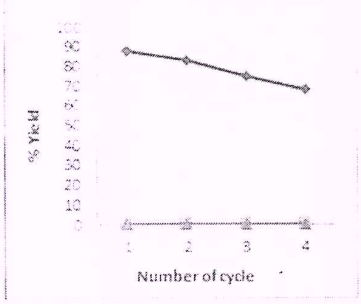

Fig 1: Variation of product yield with no. of cycles.

3.3. CONCLUSION.

It is observed that the indole is more reactive towards electrophilic substitution reaction at three positions to N-H of indole ring the effect of substituents in 1, 3-diphenyl-1H-pyrazole-4-carbaldehyde was investigated. The yield of 3-((1H-indol-3-yl)(1,3-diphenyl-1H-pyrazol-4-yl)methyl)-1H-indole derivatives in the presence of clay as catalyst is summaries in the table 1. It is observed that 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with electron withdrawing group at

Ortho and Para position to phenyl ring gives very fast reaction at room temperature as compare to 1,3-diphenyl-1H-pyrazole-4-carbaldehyde without electron withdrawing group at phenyl ring. Whenever electronic donating group is presenting at ortho and para position decreases the rate of reaction. It is also observed that time required for reaction is depending on the amount of catalyst.

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