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Design an EfficientMethod for the Synthesis of 2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*d*]imidazole

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Abstract

A simple, efficient and environmentally friendly method has been developed for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole by using Gadolinium(III) trifluoromethanesulfonate catalyst and ethanol reflux reaction conditions.By using this method,12 new 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole derivatives were synthesised under optimised reactions conditions. All these new product structures are confirmed by spectral analysis. By this method, we achieved imidazole derivatives with more operational simplicity, short reaction time and good yields (up to 85%).

Keywords*:* Gadolinium (III), Benzoimidazoles, pyrazoles, One-pot reactions, imidazoles

1. Introduction

Benzoimidazoles are important heterocyclic compounds and it is used as a core element in the constructionof diversified valuable applications[1] in the field of drug discovery and pharmaceutical chemistry such as including antimicrobial[2] and antifungal,[3] cytotoxic,[4] antidiabetic[5] applications. Further, substituted benzo

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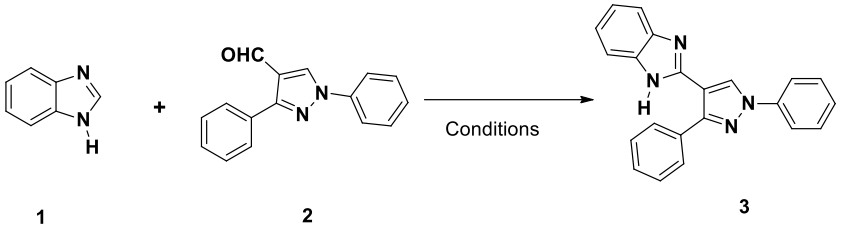
imidazoles have been designed and synthesised for biological evaluations[6]. Pyrazoles are the privileged compounds for the pharmaceutical and agricultural research,[7-12] such as Celebrex, Viagra, Zometapine, Cyenopyrafen, Fenpyroximate and Tebufenpyrad and pyrazole containing compounds in the field of medicinal chemistry such as anticancer,[13] antimicrobial and antimicrobial activities.[14-22]

2. Results and Discussion

The reaction optimisation conditions were developed for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole derivatives by using Gadolinium (III) trifluoromethanesulfonate catalyst. By the condensation of 1*H*-benzo[d]imidazole and synthesised aldehydes in the simple reaction condition, in the presence of ethanol reflux for 6h offered the final required compound in excellent yield of 85%, and then it was purified by the column chromatography.

Initially, to optimise the best reaction conditions, reactions were carried out at room temperature (RT) and also at high temperature. Such refluxed conditions were under divergent solvents of variety of polarity such as water, ethanol and methanol etc (Table 1, Entries 1-12). As mentioned in Table 1, among various synthetic attempts,it was found that under refluxed in ethanol solventconditions with Gadolinium(III) trifluoromethanesulfonateas a catalyst, 1 mmol of the reactants provided the best yield. To provide the performance of the Gadolinium(III) trifluoromethanesulfonate catalyst for the synthesis of **3a**, a blank reaction was also performed without Gadolinium(III) trifluoromethanesulfonatecatalyst in ethanol solvent using similar synthetic conditions yielded only 30 % even after 6hrs of reaction time (Table 1, Entry 7). This indicates that Gadolinium(III) trifluoromethanesulfonate catalysts play a crucial role in the synthesis of **3a.**Moreover,to understandtheeffect of a catalyst on the reaction**,** we also carried out few other reactions using different well known other similar catalysts such as HCl, acetic acid, $Na_2S_2O_5$, $Gd(OTf)_3$, $Cu(OTf)_3$, and $ZnCl_2$ etc. In fact, among all our attempts in using the above-mentioned catalysts, acetic acid provided the best yield. In this context, we can conclude that the best-optimised condition for the syntheses of

3awasGd(OTf)$_3$ catalyst of 10 mol % in ethanol solvent under refluxed synthetic conditions. Hence these optimised conditions were selected for the synthesis of various derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (**3a-l**).

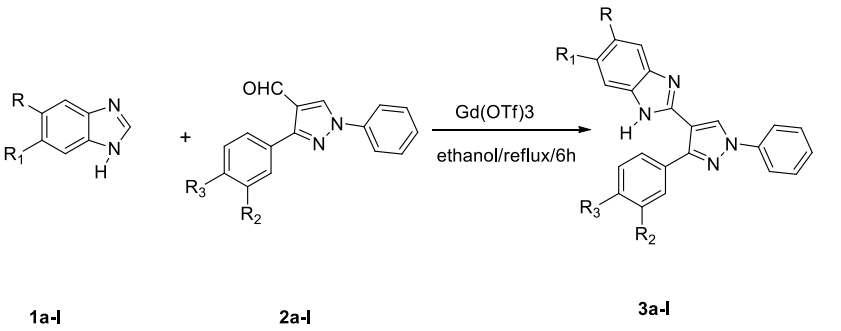


Scheme 1. Synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole using various reaction conditions.

The optimised conditionsdescribed above were employed for the synthesis of a series of 1,3-diphenyl-1H-pyrazole-4-carbaldehydesusing various electron-withdrawing and electron-donating groups. A variety of substituents in 1,3-diphenyl-1H-pyrazole-4-carbaldehyde reacted well in this synthetic protocol with reasonably good yields (69-85 %) (Table 2). Based on the above synthetic conditions, we can conclude that this methodology could tolerate effectively both the electron-withdrawing and electron-donating groups to obtain corresponding derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole(**3a-l**),with good yields. Hence, it can be concluded that this methodology can apply for a variety of substituents such as electron-withdrawing and electron-donating groups on 1,3-diphenyl-1H-pyrazole-4-carbaldehyde to yield derivatives of benzo[d]imidazole derivatives. Moreover, the catalysts employed-Gadolinium(III) trifluoromethanesulfonate is cheap and less solvent usage and less reaction time and so on are better conditions for the synthesis of derivatives (**3a-l**). So this study provides a road map for the synthesis of a variety of new drugs using cost-effective simple reaction conditions.

Table 1: Reaction conditions for 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield[a] (%)
1	-	-	RT	12	-
2	Methanol	-	RT	12	-
3	Ethanol	-	RT	12	-
4	Water	-	RT	12	-
5	CH_3CN	-	RT	12	-
6	Methanol	-	Reflux	12	25
7	Ethanol	-	Reflux	12	30
8	-	Gd(OTf)3	Reflux	6	50
9	CH_3CN	$Cu(OTf)_3$	Reflux	6	55
10	Methanol	Gd(OTf)3	Reflux	6	60
11	Ethanol	$ZnCl_2$	Reflux	6	45
12	Methanol	$Na_2S_2O_5$	RT	6	50
13	Ethanol	HCl	Reflux	6	70
15	Methanol	Acetic acid	RT	6	50
15	**Ethanol**	**$Gd(OTf)_3$**	**Reflux**	**6**	**85**



Scheme 2: Synthetic conditions for derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole.

Table 2: Reaction conditions for derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole.

Entry	Product	Yield (%)
1	3a	85
2	3b	77
3	3c	73
4	3d	70
5	3e	79
6	3f	70
7	3g	80
8	3h	72
9	3i	70
10	3j	69
11	3k	75
12	3l	69

3. Conclusion

Asimple prototype facile, efficient, mild and straightforward synthetic method for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole derivatives was developed, **3(a-l),** usingcost-effective Gadolinium(III) trifluoromethanesulfonateas a catalyst in an ethanol solvent with reasonable good yields. By using this new synthetic methodology, we achieved twelve new imidazole derivatives with more operational simplicity, less solvent usage, short reaction time and good yields. Moreover, this methodology could tolerate both electron-withdrawing and electron-donating groups more effectively for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazolederivatives, in good yields.

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5. Experimental Section

5.1 Materials and Methods

Chemical reagents used for all the syntheses were purchased from Sigma–Aldrich and used without any further purification process. All the solvents used for column chromatography and extraction were distilled beforetheir use. Silica gel plates (0.25 mm, E. Merck, 60 F254) using *p*-anisaldehyde, ninhydrin, iodine, and $KMnO_4$were used for the TLC analysis and UV lamp for the visualisation of the spots. ^1H and ^{13}C NMR experiments were performed on Bruker Avance300/500 and 75/125 MHz, respectively using downstream from the internal tetramethylsilane standard in ppm. The spin multiplicities of all the compounds are described as; 's'for singlet, 'bs'for broad singlet, 'd' for doublet, 'dd' for double doublet, 't'for triplet, 'q' for quartet and 'm' for multiplet, respectively and the coupling constants are reported in Hertz (Hz).

General synthetic procedure for the Synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole: (**3a**). Equimolar ratio of the three reactants, 1H-benzo[d]imidazole (1mmol), 1,3-diphenyl-1H-pyrazole-4-carbaldehyde were taken in round bottom flask dissolved in the presence of ethanol (10 ml), and add Gadolinium(III) trifluoromethanesulfonate catalyst then the reaction mixture refluxed for 6hrs. The reaction was monitored by TLC analysis. After completion of the reaction the solvent was removed from the crude mixture and extracted using ethyl acetate and water. The final compounds were purified by the column chromatography using silica gel by eluted with ethyl acetate and hexane (30:70) to yield 85 %. White solid, Mp: 172-175 1H NMR (300 MHz, DMSO-d6) d 8.57 (s, 1H), 7.80 - 7.71 (m, 4H), 7.54 (1 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.33 & 7.20 (m, 4H), 7.23 (d, 2H). 13C NMR (75 MHz, DMSO-d_6) d 150.1, 146.3, 137.7, 136.3, 132.8, 129.8, 128.7, 127.1, 126.7, 125.3, 120.5, 117.1, 115.2, 111.3. MS (ESI): m/z 337 [M+H]. HRMS (ESI) calcd for C22H16N4 found: 337.18.

Similar experimental procedure used for**3a,** was employed for the syntheses of the remaining derivatives, **3b-3l** withtheyields of range between, 72-85 %.

2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3b):brown Colour solid, yield 77 %, Mp: 185-

187, ^{1}H NMR (300 MHz, $CDCl_3$) d 8.53 (s, 1H), 7.70 (d, 2H), 7.69-7.70 (m, 2H), 7.60-7.49 (m, 6H), 7.27 (t, 2H), 7.03-6.93 (m, 1H). ^{13}C NMR (75 MHz, CDCl3) d 160.1, 158.9, 151.7, 147.8, 138.3, 131.3,128.4,128.9,127.1,126.8,125.6,124.4,118.1,116.5,115.0,111.7.; MS (ESI): m/z 354.38 [M+H]. HRMS (ESI) calcd for $C_{22}H_{15}N_4F$ found: 354.19.

2-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3c): light yellow solid, yield 73 %, Mp: 170-173, ^{1}H NMR (300 MHz, $CDCl_3$) 8.70 (s, 1H), 7.67 (d, J= 7.5 Hz, 2H), 7.59 (d, J = 3.1 Hz, 2H), 7.53-7.49 (m, 6H), 7.44 (d, J=7.3 Hz, 2H), 7.6 (d, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 150.7, 146.8, 138.2, 133.8, 130.3, 131.6, 130.0, 129.8, 128.2, 127.4, 127.1, 126.5, 125.1, 120.3, 119.8, 117.8, 113.6, 23.6.; MS (ESI): m/z 351 [M+H]. HRMS (ESI) calcd for $C_{23}H_{18}N_4$ [found: 351.11.

2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3d): yellow solid, yield 70 %, Mp: 189-190, 1HNMR (400 MHz, $CDCl_3$) d 8.57 (s, 1H), 7.80-7.75 (m, 2H), 7.70 (d,J = 5.8, Hz, 2H), 7.63-7.54 (m, 6H), 7.44 (t, J= 7.5 Hz, 2H),6.88 (d, J= 2.4 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, CDCl3)157.5, 151.3, 146.6, 138.1, 133.2, 130.6, 129.8, 128.0, 127.7, 126.9,125.4, 125.9, 119.6, 119.3, 117.8, 115.9, 111.2, 56.8.; MS (ESI): m/z 366[M+H]þ. HRMS (ESI) calcd for $C_{23}H_{18}ON_4$ found: 366.50.

6-chloro-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3e): Yellow solid, yield 79%, Mp: 188-190, ^{1}H NMR (300 MHz, CDCl3) 8.37 (s, 1H), 7.72 (d,

J = 7.64 Hz, 2H), 7.50-7.39 (m, 4H), 7.26-7.14 (m, 3H), 7.18 (d, J = 7.6 Hz, 1H), 6.56 (d, J = 8.5 Hz, 2H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) 161.1, 157.7, 146.0, 138.2, 131.5, 127.4, 127.1, 126.7, 126.01, 124.3, 123.1, 118.4, 114.4, 112.5, 56.2.; MS (ESI): m/z 401 [M+H]. HRMS (ESI) calcd for $C_{23}H_{17}ON_4Cl$, found: 400.14.

6-fluoro-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3f): brown solid, yield 70 %, Mp: 171-174, ^{1}H NMR (500 MHz, $CDCl_3$) 8.74 (s, 1H), 7.83 (d, J= 7.9 Hz, 2H), 7.73 (d, J= 8.44 Hz, 2H), 7.57-7.43 (m, 4H), 7.39 (t, J = 7.4 Hz, 1H), 7.02-6.85 (m, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.2, 160.9, 159.3, 151.7, 148.2, 140.3, 139.6, 129.7, 128.1, 121.8, 120.6, 119.8,

117.9, 113.3, 118.6, 110.2, 54.1.; MS (ESI): m/z 384 [M+H] ; HRMS (ESI) calcd for $C_{23}H_{17}ON_4F$ found: 384.56.

2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-fluoro-1H-benzo[d]imidazole (3g):brown Colour solid, yield 80 %, Mp: 187-190, ^{1}H NMR (300 MHz, $CDCl_3$) d 8.54 (s, 1H), 7.60 (d, 2H), 7.59-7.70 (m, 2H), 7.50-7.49 (m, 6H), 7.27 (t, 2H), 7.03-6.63 (m, 1H). ^{13}C NMR (75 MHz, CDCl3):δ 161.1, 159.9, 152.7, 148.8, 139.3, 132.3,129.4,128.9,128.1,126.8,125.6,124.4,119.1,118.5,116.0,112.7.; MS (ESI): m/z 354 [M+H]. HRMS (ESI) calcd for $C_{22}H_{15}N_4F$ found: 354.43.

2-(1,3-diphenyl-1H-pyrazol-4-yl)-6-chloro-1H-benzo[d]imidazole (3h): Light White solid, yield 72%, Mp: 191-193, ^{1}H NMR (300 MHz, CDCl3) 8.77 (s, 1H), 7.67 (d, J =7.5 Hz, 2H), 7.78 (d, J = 6.5, 3.0 Hz, 2H), 7.55-7.42 (m, 6H), 7.45 (t, J =7.4 Hz, 2H), 7.20 (d, J =7.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6), 151.1, 148.4, 139.2, 132.4, 129.8, 127.7, 127.1, 126.6, 126.31, 123.6, 116.1, 112.8, 110.4.; MS (ESI): m/z 371 [M +H] . HRMS (ESI) calcd for $C_{22}H_{15}N_4Cl$, 370.10; found: 370.04.

6-chloro-2-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3i): yellow solid, yield 70 %, Mp: 173-176, ^{1}H NMR (300 MHz, $CDCl_3$), 8.58 (s, 1H), 7.73 (d, J= 7.6 Hz, 2H), 7.53 (d, J= 8.4 Hz, 2H), 7.40-7.32 (m, 7H), 7.18 (d, J = 8.22 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, CDCl3), 149.1, 146.1, 139.0, 133.6, 131.4, 130.0, 128.6, 128.1, 127.0, 125.7, 122.3, 116.5, 1112.9, 20.4.; MS (ESI): m/z 385 [M+H]. HRMS (ESI) calcd for $C_{23}H_{17}ClN_4$ found: 385.23.

5,6-dichloro-2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3j): Light red solid, yield 69 %, Mp: 206-209, ^{1}H NMR (500 MHz, $CDCl_3$) 8.63 (s, 1H), 7.85 (d, J =7.7 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.63 (s, 2H), 7.19 (d, J = 5.1 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 6.95-6.76 (m, 2H), 3.71 (s, 3H).^{13}C NMR (75 MHz, CDCl3) 152.3, 151.3, 149.0, 137.8, 128.2, 129.1, 126.5, 123.7, 122.2, 118.2, 113.1, 111.8, 54.7.; MS (ESI): m/z 435 [M+H]. HRMS (ESI) calcd for $C_{23}H_{16}ON_4Cl_2$ found: 435.07502.

6-chloro-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (3k): White solid, yield 75 %, Mp: 191-195, ^{1}H NMR (300 MHz, $CDCl_3$) 8.72 (s, 1H), 7.55 (d,J = 7.7 Hz, 2H), 7.69-7.52 (m, 2H), 7.44-7.45 (m, 3H), 7.38-7.31 (m,2H), 7.13e7.09 (m, 2H),

6.10 (t, J= 8.5 Hz, 1H); 13C NMR (75 MHz, CDCl3) 161.5, 160.3,148.1, 145.4, 138.0, 137.8, 135.0, 129.4,128.2, 127.8, 126.7, 122.3, 118.0, 114.5, 113.2, 109.1; MS (ESI): m/z 389 [M+H]. HRMS (ESI) calcd for $C_{22}H_{14}ClFN_4$ found: 389. 07.

2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-1H-benzo[d]imidazole (3l): brown solid, yield 69 %, Mp: 183-185, 1H NMR (500 MHz, CDCl3) 8.45 (s, 1H), 7.68-7.59 (m, 4H), 7.40 (d, J =7.3 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.38-7.32 (m, 2H), 7.06 (d, J = 8.2,Hz, 1H), 6.88 (t, J = 8.49 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) 165.1, 164.1, 148.8, 146.23, 139.3, 132.8, 130.1, 130.3, 128.5, 127.8, 127.4, 127.1, 124.4, 119.0, 115.4, 115.1, 112.8, 21.9.; MS (ESI): m/z 368 [M+H]. HRMS (ESI) calcd for $C_{23}H_{17}FN_4$ found: 368.15

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