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

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Abstract

A simple, highly 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 synthesized under optimized reactions conditions. All these new products 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's with in their usage as a core construction for multiple and valuable applications[1] in the area of drug discovery and medicinical and argo chemistry such as including antimicrobial[2] and antifungal,[3] cytotoxic,[4] and antidiabetic[5] applications and also substituted benzo imidazoles have been designed and synthesized for biological

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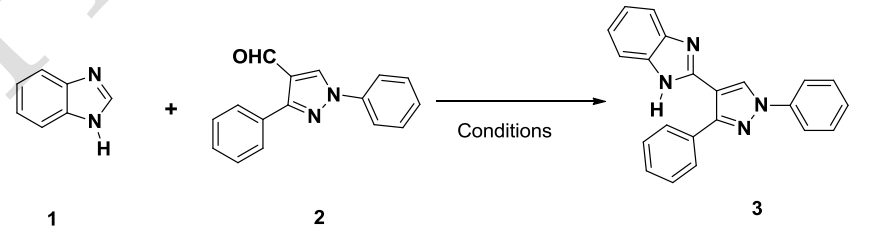
evaluations[6]. Pyrazoles are the privileged compounds for the pharmaceutical and agricultural research,[7-12] such as Celebrex, Viagra, Zometapine, Cyenopyrafen, Fenpyroximate and Tebufenpyrad and pyrazole containing compounds with in the field of medicinal and agro chemistry like antimicrobial acivities.[13-22]

2. Results and discussion

The reaction optimization conditions was 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 synthesized aldehydes in the simple reaction condition, in the presence of ethanol reflux for 6h offered the final required compound in excellent yield 85%, and then it was purified by the column chromatography.

Initially to optimize the reaction conditions, we administered the reactions at the RT conditions and also as at refluxed conditions under different polar solvents (Table 1, Entries 1-12) like water, methanol and ethanol etc. In our various attempts as mentioned in table 1, we found that under refluxed conditions in ethanol solvent with Gadolinium(III) trifluoromethanesulfonate is as a catalyst, 1 mmol of the reactants provided the good and simplest yield. So as to determine the effectiveness of the Gadolinium(III) trifluoromethanesulfonate catalyst for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (**3a**), a test reaction was performed without Gadolinium(III) trifluoromethanesulfonate catalyst in ethanol solvent using similar reactants under refluxed conditions yielded only 30 % even after 6hrs (Table 1, Entry 7).



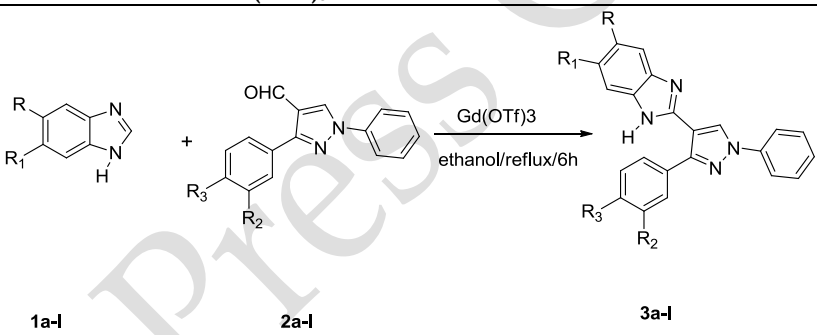
Scheme 1. Synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole using various reaction conditions.

We also administered few model reactions to see viability of the reaction using different well known other catalysts like Ethanoicacid, HCl, $Na_2S_2O_5$, $Gd(OTf)_3$, $Cu(OTf)_3$, and $ZnCl_2$ etc. Among all our attempts using different catalysts, $Gd(OTf)_3$ provided the best yield. The simplest optimized conditions were 10 mol % of $Gd(OTf)_3$ in ethanol solvent under refluxed conditions. During this context, these optimized conditions were employed for the synthesis of derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d] imidazole (**3a-l**).

The optimized reaction conditions described above were employed for a series of substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde including electron-withdrawing and electron-donating groups. A variety number of substituents in 1,3-diphenyl-1H-pyrazole-4-carbaldehyde reacted well during in this protocol and delivered good yields (69-85 %) (Table 2). From the above results we will concluded that, this system can tolerate both electron-withdrawing and electron-donating groups effectively for the synthesis of corresponding derivatives of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole in good yields. Hence, this system can apply generally for sort of substituents on 1,3-diphenyl-1H-pyrazole-4-carbaldehyde to yield derivatives of benzo[d]imidazole derivatives with good yield for reasonable Gadolinium(III) trifluoromethanesulfonate catalyst, less solvent and low reaction time etc. This study provides a road map for the synthesis of new drug molecules by simple direct one pot method (see supporting information for the spectral data).

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

3.

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

Conclusion

In summary, we've been developed a proto type facile and efficient, mild and easy method for the synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole, **3(a-l),** by using Gadolinium(III) trifluoromethanesulfonate as a catalyst in ethanol solvent by this new synthetic method, we achieved 12 new imidazole derivatives with more operational simplicity, low reaction time and good yields (up to 85 %). Moreover, this system can also tolerate both electron-withdrawing and electron-donating groups effectively for the synthesis of corresponding derivatives of **3(a-l)**, in good yields.

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Experimental Section

Materials and methods

Chemical reagents were purchased from Sigma–Aldrich and were used without further purification. Solvents for extraction and column chromatography were distilled prior to use. TLC analysis were performed with silica gel plates (0.25 mm, E. Merck, 60 F254) using ninhydrine, *p*-anisaldehyde, $KMnO_4$, iodine, and UV lamp for visualization. ^1H and ^{13}C NMR experiments were performed on 300 or 500 and 75 or 125 MHz respectively, on a Bruker Avance. Chemical shifts are reported in parts per million (ppm) downstream from the internal tetramethylsilane standard. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants are reported in Hertz (Hz).

General 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. After completion of the reaction the solvent was removed from crude mixture and extracted with 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 %. light 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-d6) 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 of **3a** was employed for all the remaining derivatives, **3b-3l** with yields 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, ^1H 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, 1H NMR (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, CDCl3), 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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