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Oxidative cyclization of thiophenolic and phenolic Schiff's bases promoted by PCC: a new oxidant for 2-substituted benzothiazoles and benzoxazoles

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Abstract

Pyridinium chlorochromate (PCC) supported on silica gel effects the oxidative cyclization of structurally diverse thiophenolic and phenolic Schiff's bases, thereby providing an efficient and convenient method for the synthesis of a library of 2-arylbenzothiazoles and 2-arylbenzoxazoles.

1. Introduction

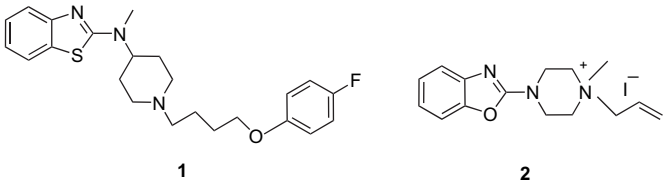
Benzothiazoles and benzoxazoles are a class of molecules that possess an array of biological properties.[1] In particular, benzothiazole **1** acts as a Ca^{2+} channel antagonist,[2] and benzoxazole **2** acts as a $5HT_3$ receptor partial agonist,[3] (Fig. 1). Although a wide range of methods are available for synthesizing benzothiazole[4] and benzoxazole,[5] a real need exists for new procedures that support many kinds of structural diversity and various substitution patterns in the target library.

In general benzothiazoles are synthesized by condensation of 2-aminobenzenethiol with carboxylic acid derivatives,[6] the base induced cyclization of the corresponding 2-haloanilides,[7] or the radical cyclization of thioacylbenzanilides.[8,9] On the other hand the most common synthetic approach to 2-arylbenzoxazoles involves (1) coupling of carboxylic acids with 2-aminophenols by dehydration catalyzed by strong acid;[10] and (2) the oxidative cyclization of phenolic Schiff's bases, derived from the condensation of 2-aminophenols and aldehydes, using various oxidants such as $PhI(OAc)_2$,[11] $Mn(OAc)_3$,[12] $ThClO_4$,[13] $Ba(MnO_4)_2$,[14] NiO_2,[15] and $Pb(OAc)_4$.[16] All the above methods have limited applications for the synthesis of either benzothiazoles or benzoxazoles. As part of our current interest in oxidation processes,[17] we sought PCC[18] as an effective oxidant for the oxidative cyclization of both thiophenolic and phenolic Schiff's bases to the corresponding 2-arylbenzothiazole and benzoxazole.

2. Result and discussion

2.1. Efficacy of different oxidants on the oxidative cyclization

Even though PCC has been used for various oxidation processes,[18,19] it was under-utilized for oxidative cyclization reactions. We have explored the possibility of utilizing PCC as an oxidant for the oxidative cyclization of Schiff's base **3**.



1 **2**

Figure 1.

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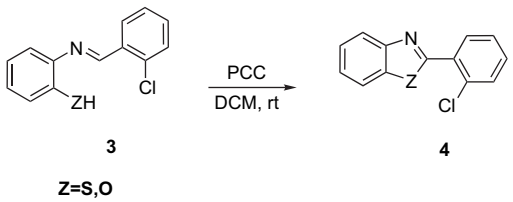
Our initial studies on the reaction of Schiff's base **3** with PCC/SiO_2 in dichloromethane at room temperature afforded the compound **4** in excellent yield at a short reaction time.

To assess the efficacy of PCC over different oxidants the oxidative cyclization of Schiff's base **3** with different oxidants was performed. Dichloromethane was used as the solvent for all reactions. The results revealed that $FeCl_3$ led to the formation of 2-(2-chlorophenyl)-1,3-benzoxa(thia)zole in low yields. MnO_2 led to the formation of benzoxazole in low yield, but it failed to form benzothiazole. $CuCl_2$ and molecular iodine, respectively, led to the formation of the desired products in moderate yield and IBX in CH_2Cl_2 completely failed to oxidize the substrates. Thus it is obvious from this study that the oxidizing performance of PCC was superior in this oxidative cyclization protocol (Scheme 1; Table 1).



Scheme 1.

2.2. Synthesis of 2-arylbenzoxa(thia)zole

The generality of the transformation of thiophenolic and phenolic Schiff's bases to the corresponding benzothiazole and benzoxazole was checked by treating PCC with a range of substituted and structurally diverse Schiff's bases. Treatment of Schiff's bases **5** bearing different substituents with silica gel supported PCC (1.1 equiv) in CH_2Cl_2 afforded the oxidized products in good to excellent yields (Scheme 2; Table 2).The results revealed that, the substrates bearing electron releasing functionalities afforded comparitively low yields of products (Table 2; entries 3–5). This observation was in good agreement with other oxidative cyclization protocols.

On the basis of the above results, coupled with the fact that benzoxa(thia)zoles and pyrazoles[20] are often associated with important biological properties, we extended our methodology for the oxidative cyclization of Schiff's bases of formyl pyrazoles **7**.[21]

However, these substrates toward cyclization had shown lesser reactivity as indicated by longer reaction times and lower yields (Scheme 3, Table 3). This may be due to the

Table 1
Effect of different oxidants on the oxidative cyclization of Schiff's base **3**

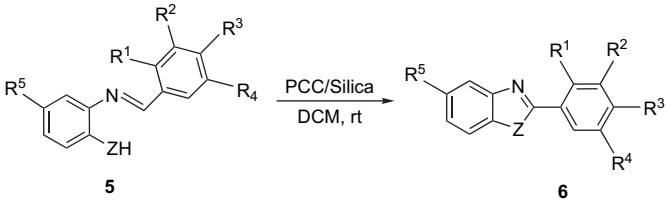
Entry	Oxidant	Equiv	Time (h)	Z=S[a] (%)	Z=O[a] (%)
1	$FeCl_3$	1.1	2.0	15	10
2	MnO_2	1.0	1.0	0	15
3	IBX	1.0	3.0	0	0
4	PCC	1.1	0.5	89	91
5	$CuCl_2$	1.0	1.0	50	39
6	I_2	1.0	1.0	42	51

[a] Isolated yield.

Table 2
PCC mediated synthesis of 2-phenylbenzoxa(thia)zoles

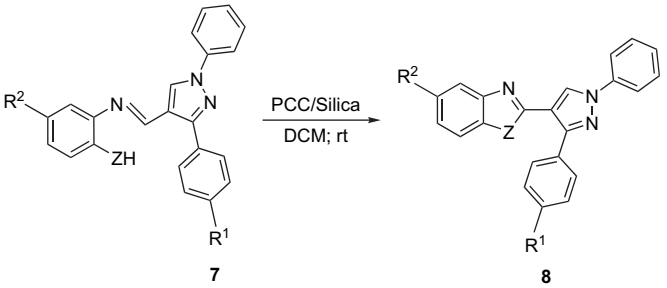
Entry	Z	R^1	R^2	R^3	R^4	R^5	Time (min)	Product[a]	Yield[b] (%)
1	S	Cl	H	H	H	H	20	**6a**	89
2		H	NO_2	H	H	H	15	**6b**	82
3		H	OMe	OBn	H	H	45	**6c**	78
4		H	OMe	OBn	OMe	H	35	**6d**	75
5		H	Br	OH	OMe	H	30	**6e**	74
6	O	Cl	H	H	H	H	30	**6f**	91
7		H	H	NO_2	H	Me	20	**6g**	89
8		Cl	H	H	H	Me	15	**6h**	91
9		NO_2	H	H	H	Me	15	**6i**	88
10		H	NO_2	H	H	Cl	25	**6j**	89

[a] All the products were characterized by IR, NMR, and mass spectroscopies.
[b] Isolated yield.



Scheme 2.

presence of bulky phenyl group at the C_3 atom of the pyrazole ring, which may hinder cyclization (Table 3).



Scheme 3.

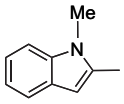
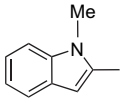
To extend the applicability further, we focussed our attention on the synthesis of indolyl and pyrrolyl benzoxa(thia)-zoles (Scheme 4), which had been shown to possess cytotoxic activity.[22] Here too the reaction requires longer reaction time, but the yield of the products were fairly high (Table 4) as compared to pyrazolyl benzoxa(thia)zoles.

Table 3
PCC mediated synthesis of 2-pyrazolyl benzoxa(thia)zoles

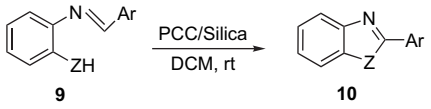
Entry	Z	R^1	R^2	Time (min)	Product[a]	Yield[b] (%)
1	S	Br	H	50	**8a**	74
2		OEt	H	40	**8b**	70
3		Cl	H	45	**8c**	68
4		OMe	H	40	**8d**	72
5	O	OEt	H	55	**8e**	72
6		Cl	H	30	**8f**	81
7		Br	Me	30	**8g**	69

[a] All the products were characterized by IR, NMR, and mass spectroscopies.
[b] Isolated yield.

Table 4
PCC mediated synthesis of 2-indolyl and pyrollyl benzoxa(thia)zoles

Entry	Z	Ar	Time (min)	Product[a]	Yield[b] (%)
1	S		45	**10a**	88
2	O		45	**10b**	83
3	O		40	**10c**	80

[a] All the products were characterized by IR, NMR, and mass spectroscopies.
[b] Isolated yield.



9 **10**

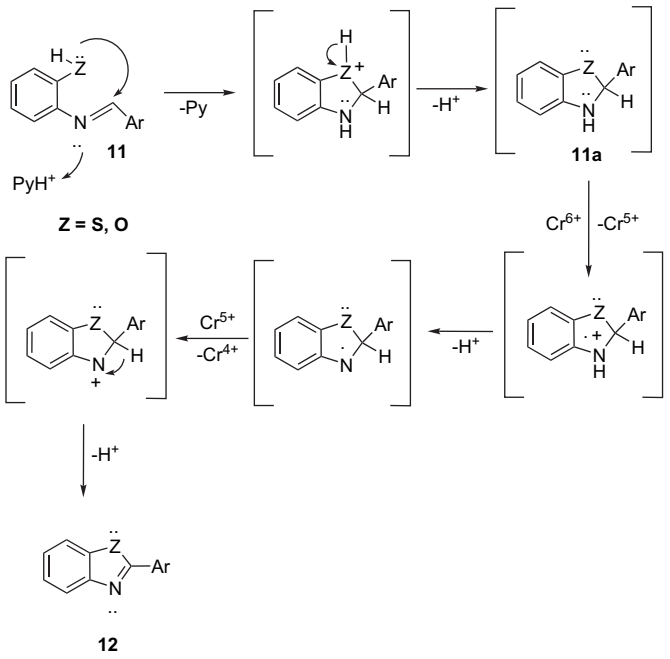
Scheme 4.

The intramolecular cyclization of phenolic and thiophenolic Schiff's bases was characterized by the absence of C*H*=N proton signal at δ 8.3–8.8 ppm (except, compounds **8a–8g**, where a singlet at this region is observed due to the C_5-*H* proton in the pyrazole ring).

The formation of the product was further supported by the disappearance of 3360 cm^{-1} (O–H stretch) and 2250 cm^{-1} (S–H stretch) peaks in the IR spectra.

2.3. Mechanism

A mechanistic rationale portraying the probable sequence of events is given in Scheme 5. The formation of **12** from **11** can be rationalized through the intermediacy of 2-aryl-2,3-dihydro-1,3-benzoxa(thia)zole (**11a**), which may be formed by an initial attack of pyridinium ion on the imino nitrogen atom, followed by deprotonation. The subsequent attack of Cr^{6+} on the nitrogen atom results in dehydrogenation to afford **12**.



Scheme 5. Proposed mechanism.

3. Conclusion

In summary, the present procedure involving PCC mediated oxidative cyclization of a wide range of phenolic and thiophenolic Schiff's bases provides a convenient and synthetically useful method for the preparation of 2-arylbenzoxa(thia)zoles. The oxidative cyclizing performance of PCC is noteworthy, since it is capable of oxidizing both phenolic and thiophenolic Schiff's bases in good to excellent yields. The applications of this new methodology to the synthesis of other heterocycles are actively underway.

4. Experimental section

4.1. General

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer FTIR spectrophotometer as KBr pellets. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard on a JEOL spectrometer at 500 and 125 MHz, respectively. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI mass spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey–Nagel, Germany).

4.2. Preparation of silica supported PCC

The solid supported PCC was prepared by a procedure reported by Vanden Eynde et al.[19] Silica gel 100–200 mesh (200 g) was added to a solution of PCC (45 g; 200 mmol) in acetone (200 mL) and stirred well for 3 h. The solvent was evaporated under reduced pressure and the resulting solid was dried at 100 °C for 2 h and used.

4.3. Preparation of phenolic and thiophenolic Schiff's bases

Schiff's bases were prepared by refluxing a solution of appropriate aldehyde (20.0 mmol) and *o*-aminophenols/*o*-aminothiophenol (30.0 mmol) in methanol (10 mL) for 4–5 h. The solid product thus obtained was filtered off and washed with ice-cold methanol (5 mL) in portions and dried.

4.4. Typical procedure for the preparation of 2-arylbenzoxa(thia)zoles

Schiff's base (2.0 mmol) was rapidly added to a stirred suspension of silica supported PCC (2.2 mmol corresponding to

PCC) in dichloromethane. The mixture was stirred at room temperature for the specified time (see Tables 2–4). After completion of the reaction as indicated by TLC (petroleum ether/ethyl acetate), the reaction mixture was filtered on a thin Celite pad. The filtrate was concentrated, poured into water, and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/ethyl acetate to give product.

*4.4.1. 2-(2-Chlorophenyl)-1,3-benzothiazole (**6a**)*

Colorless solid; mp 71–73 °C; R_f=0.39 (AcOEt/petroleum ether 10%). IR (KBr): 3053, 2359, 1559, 1454, 1429, 1316, 1270, 1059, 965, 749, 726 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.38–7.44 (m, 3H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.93 (d, 1H, J=7.6 Hz, Ar-H), 8.13 (d, 1H, J=8.4 Hz, Ar-H), 8.20–8.21 (m, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 121.5, 123.6, 125.6, 126.4, 127.2, 130.9, 131.3, 131.9, 132.4, 132.8, 136.2, 152.6, 164.3. MS (EI): m/z=245 [M^+], 247 [M^{+2}]. Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.44; H, 3.33; N, 5.67.

*4.4.2. 2-(3-Nitrophenyl)-1,3-benzothiazole (**6b**)*

Colorless solid; mp 181–183 °C; R_f=0.50 (AcOEt/petroleum ether 30%). IR (KBr): 3402, 2937, 1529, 1461, 1347, 1107, 1048, 731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.42 (t, 1H, J=7.6 Hz, Ar-H), 7.51 (t, 1H, J=7.6 Hz, Ar-H), 7.65 (t, 1H, J=7.6 Hz, Ar-H), 7.92 (d, 1H, J=7.6 Hz, Ar-H), 8.09 (d, 1H, J=7.6 Hz, Ar-H), 8.30 (dd, 1H, J=6.9, 9.2 Hz, Ar-H), 8.38 (d, 1H, J=7.6 Hz, Ar-H), 8.90 (s, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 121.9, 122.4, 123.8, 125.2, 126.1, 126.9, 130.2, 133.1, 135.3, 135.4, 148.8, 154.0, 164.9. MS (EI): m/z=256 [M^+]. Anal. Calcd for $C_{13}H_8N_2SO_2$: C, 60.92; H, 3.15; N, 10.93. Found: C, 60.75; H, 3.22; N, 10.89.

*4.4.3. 2-[4-(Benzyloxy)-3-methoxyphenyl]-1,3-benzothiazole (**6c**)*

Colorless solid; mp 97–99 °C; R_f=0.63 (AcOEt/petroleum ether 30%). IR (KBr): 3468, 2937, 1630, 1264, 1141, 997 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.94 (s, 3H, $-OCH_3$), 5.22 (s, 2H, $-OCH_2C_6H_5$), 6.93 (d, 1H, J=8.4 Hz, Ar-H), 7.31–7.39 (m, 4H, Ar-H), 7.42–7.48 (m, 3H, Ar-H), 7.51 (dd, 1H, J=2.3, 8.4 Hz, Ar-H), 7.72 (d, 1H, J=2.3 Hz, Ar-H), 7.85 (d, 1H, J=7.6 Hz, Ar-H), 8.01 (d, 1H, J=8.4 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.3, 71.0, 110.3, 113.5, 121.1, 121.6, 122.9, 124.9, 126.3, 127.1, 127.3, 128.1, 128.8, 134.9, 136.6, 149.9, 150.7, 154.2, 168.1. MS (EI): m/z=349 [M^+]. Anal. Calcd for $C_{20}H_{17}NSO$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.49; H, 4.82; N, 3.99.

*4.4.4. 2-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-1,3-benzothiazole (**6d**)*

Brown solid; mp 77–79 °C; R_f=0.58 (AcOEt/petroleum ether 30%). IR (KBr): 3432, 2915, 2369, 1623, 1590, 1406, 1329, 1240, 1118, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.93 (s, 6H, $-OCH_3$), 5.09 (s, 2H, $-OCH_2C_6H_5$), 7.29–7.38 (m, 6H, Ar-H), 7.46–7.50 (m, 3H, Ar-H), 7.86 (d, 1H, J=7.6 Hz, Ar-H), 8.04 (d, 1H, J=8.4 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.2, 76.9, 104.9, 121.7, 123.1, 125.2, 126.4, 128.1, 128.3, 128.6, 129.3, 135.1, 137.6, 139.5. MS (EI): m/z=377 [M^+]. Anal. Calcd for $C_{22}H_{19}NSO_3$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.89; H, 4.99; N, 3.82.

*4.4.5. 4-(1,3-Benzothiazol-2-yl)-2-bromo-6-methoxyphenol (**6e**)*

Colorless solid; mp 184–186 °C; R_f=0.46 (AcOEt/petroleum ether 30%). IR (KBr): 3447, 2922, 1510, 1416, 1292, 1183, 1022, 831, 722 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ_H 3.93 (s, 3H, $-OCH_3$), 7.39 (d, 1H, J=7.6 Hz, Ar-H), 7.49–7.50 (m, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.97–8.07 (m, 2H, Ar-H), 10.32 (s, 1H, $-OH$). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 56.9, 109.7, 110.2, 122.8, 123.1, 124.1, 125.5, 125.8, 127.2, 134.9, 147.4, 149.2, 153.9, 166.5. MS (EI): m/z=335 [M^+], 337 [M^{+2}]. Anal. Calcd for $C_{14}H_{10}BrNO_2S$: C, 50.01; H, 3.00; N, 4.17. Found: C, 49.89; H, 3.09; N, 4.10.

*4.4.6. 2-(2-Chlorophenyl)-1,3-benzoxazole (**6f**)*

Colorless solid; mp 61–64 °C; R_f=0.53 (AcOEt/petroleum ether 30%). IR (KBr): 2953, 1537, 1430, 1253, 1194, 1022, 806, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.36–7.46 (m, 4H, Ar-H), 7.56–7.57 (m, 1H, Ar-H), 7.61–7.62 (m, 1H, Ar-H), 7.84–7.86 (m, 1H, Ar-H), 8.13 (dd, 1H, J=7.6, 2.3 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.9, 120.6, 124.8, 125.7, 126.2, 127.1, 131.5, 131.9, 132.0, 133.6, 141.8, 150.6, 161.1. MS (EI): m/z=229 [M^+], 231 [M^{+2}]. Anal. Calcd for $C_{13}H_6ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 68.11; H, 3.62; N, 5.99.

*4.4.7. 5-Methyl-2-(4-nitrophenyl)-1,3-benzoxazole (**6g**)*

Pale yellow solid; mp 218–250 °C; R_f=0.44 (AcOEt/petroleum ether 30%). IR (KBr): 3402, 1556, 1521, 1342, 854, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.50 (s, 3H, $-CH_3$), 7.22 (d, 1H, J=8.4 Hz, Ar-H), 7.48 (d, 1H, J=8.4 Hz Ar-H), 7.59 (s, 1H, Ar-H), 8.35–8.41 (m, 4H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.6, 110.4, 120.5, 124.3, 127.6, 128.4, 133.0, 135.3, 142.2, 149.4, 160.8, 162.7. MS (EI): m/z=254 [M^+]. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.32; H, 4.10; N, 10.92.

*4.4.8. 2-(2-Chlorophenyl)-5-methyl-1,3-benzoxazole (**6h**)*

Colorless solid; mp 74–76 °C; R_f=0.59 (AcOEt/petroleum ether 25%). IR (KBr): 2921, 1734, 1590, 1548, 1468, 1423, 1325, 1263, 1194, 1019, 774, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.49 (s, 3H, $-CH_3$), 7.18 (d, 1H, J=8.4 Hz, Ar-H), 7.38 (m, 2H, Ar-H), 7.47 (d, 1H, J=8.4 Hz, Ar-H), 7.54 (d, 1H, J=9.2 Hz, Ar-H), 7.62 (s, 1H, Ar-H), 8.11 (d, 1H, J=8.4 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.6, 110.2, 120.4, 123.5, 126.5, 126.8, 126.9, 131.4, 131.9, 133.5, 134.6, 141.9, 148.9, 161.1. MS (EI): m/z=245 [M^+], 247 [M^{+2}]. Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.22; H, 4.25; N, 5.88.

*4.4.9. 5-Methyl-2-(2-nitrophenyl)-1,3-benzoxazole (**6i**)*

Pink solid; mp 134–136 °C; R_f=0.49 (AcOEt/petroleum ether 30%). IR (KBr): 3431, 2915, 1542, 1480, 1374, 1196, 1044, 800, 772 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.48 (s, 3H, $-CH_3$), 7.19 (d, 1H, J=8.4 Hz, Ar-H), 7.42 (d, 1H, J=8.4 Hz, Ar-H), 7.58 (s, 1H, Ar-H), 7.65 (t, 1H, J=7.6 Hz, Ar-H), 7.71 (t, 1H, J=7.6 Hz, Ar-H), 7.86 (d, 1H, J=7.6 Hz, Ar-H), 8.11 (d, 1H, J=7.6 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.61, 110.40, 120.57, 121.69, 124.26, 127.30, 131.81, 132.43, 134.97, 141.78, 149.22, 149.37, 158.92. MS (EI): m/z=254 [M^+]. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.00; H, 4.02; N, 10.89.

*4.4.10. 5-Chloro-2-(3-nitrophenyl)-1,3-benzoxazole (**6j**)*

Colorless solid; mp 184–186 °C; R_f=0.52 (AcOEt/petroleum ether 30%). IR (KBr): 3424, 2361, 1526, 1449, 1351, 1100, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.38 (q, 1H, J=8.4 Hz, Ar-H), 7.54 (d, 1H, J=9.1 Hz, Ar-H), 7.72 (d, 1H, J=8.4 Hz, Ar-H), 7.78 (s, 1H, Ar-H), 8.39 (d, 1H, J=8.8 Hz, Ar-H), 8.55 (d, 1H, J=7.6 Hz, Ar-H), 9.07 (s, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 111.8, 120.5, 122.7, 126.3, 126.5, 130.4, 130.7, 133.3, 142.9, 149.5, 157.5, 161.9. MS (EI): m/z=274 [M^+], 276 [M^{+2}]. Anal. Calcd for $C_{13}H_7ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.75; H, 2.49; N, 10.15.

*4.4.11. 2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]-1,3-benzothiazole (**8a**)*

Colorless solid; mp 200–202 °C; R_f=0.47 (AcOEt/petroleum ether 25%). IR (KBr): 3359, 1637, 1554, 1506, 1406, 1222, 1085, 829, 754, 684 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.35–7.37 (m, 2H, Ar-H), 7.46–7.51 (m, 3H, Ar-H), 7.58 (d, 2H, J=8.4 Hz, Ar-H), 7.66 (d, 2H, J=8.4 Hz, Ar-H), 7.80 (d, 3H, J=8.4 Hz, Ar-H), 8.00 (d, 1H, J=8.4 Hz, Ar-H), 8.59 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 117.2, 119.5, 121.5, 122.8, 123.6, 125.1, 126.4, 127.5, 128.7, 129.7, 131.0, 131.2, 131.28, 131.7, 139.3, 151.0, 153.4, 154.2, 154.9. MS (EI): m/z=431 [M^+], 433 [M^{+2}]. Anal. Calcd for $C_{22}H_{13}N_3SBr$: C, 61.12; H, 3.26; N, 9.72. Found: C, 61.00; H, 3.33; N, 9.77.

*4.4.12. 2-[3-(4-Ethoxyphenyl)-1-phenyl-1H-pyrazole-4-yl]-1,3-benzothiazole (**8b**)*

Pale yellow solid; mp 152–154 °C; R_f=0.50 (AcOEt/petroleum ether 30%). IR (KBr): 3434, 2965, 1613, 1558, 1503, 1247, 1106, 1043, 812 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.46 (t, 3H J=7.5 Hz, $-OCH_2CH_3$), 4.10 (q, 2H J=6.8 Hz, $-OCH_2CH_3$), 6.98 (d, 2H, J=8.6 Hz, Ar-H), 7.31 (q, 2H, J=8.0 Hz, Ar-H), 7.44–7.50 (m, 3H, Ar-H), 7.62–7.66 (m, 2H, Ar-H), 7.76 (d, 1H, J=8.0 Hz, Ar-H), 7.81 (d, 2H, J=8.6 Hz, Ar-H), 7.99 (d, 1H, J=8.0 Hz, Ar-H), 8.64 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.9, 63.6, 114.5, 117.4, 119.4, 121.5, 122.6, 124.1, 124.9, 126.2, 127.3, 128.1, 129.7, 131.1, 135.1, 139.5, 152.2, 153.2, 159.9, 163.2. MS (EI): m/z=397 [M^+]. Anal. Calcd for $C_{24}H_{19}N_3OS$: C, 72.52; H, 4.82; N, 10.57. Found: C, 72.67; H, 4.75; N, 10.22.

*4.4.13. 2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-1,3-benzothiazole (**8c**)*

Colorless solid; mp 173–175 °C; R_f=0.45 (AcOEt/petroleum ether 25%). IR (KBr): 3421, 1599, 1502, 1388, 1203, 1067, 932, 823 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.33–7.37 (m, 2H, Ar-H), 7.43–7.51 (m, 5H, Ar-H), 7.72 (d, 2H, J=8.4 Hz, Ar-H), 7.79–7.82 (m, 3H, Ar-H), 8.00 (d, 1H, J=8.4 Hz, Ar-H), 8.59 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 117.3, 119.4, 121.5, 122.8, 125.1, 126.4, 127.5, 128.7, 128.8, 129.7, 130.6, 131.0, 135.0, 135.2, 139.3, 150.9, 153.4, 159.8. MS (EI): m/z=388 [M^+], 390 [M^{+2}]. Anal. Calcd for $C_{22}H_{14}ClN_3S$: C, 68.12; H, 3.64; N, 10.83. Found: C, 67.99; H, 3.76; N, 10.90.

*4.4.14. 2-[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-1,3-benzothiazole (**8d**)*

Colorless solid; mp 167–169 °C; R_f=0.44 (AcOEt/petroleum ether 30%). IR (KBr): 3402, 2346, 1609, 1558, 1505, 1406, 1248, 1034, 833, 755 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.87 (s, 3H, $-OCH_3$), 6.99 (d, 2H, J=8.4 Hz, Ar-H), 7.32 (q, 2H, J=7.6 Hz, Ar-H), 7.44–7.48 (m, 3H, Ar-H), 7.66 (d, 2H, J=8.4 Hz, Ar-H), 7.76 (d, 1H, J=7.6 Hz, Ar-H), 7.81 (d, 2H, J=7.6 Hz, Ar-H), 7.99 (d, 1H, J=8.4 Hz, Ar-H), 8.63 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 55.4, 114.0, 117.4, 119.4, 121.5, 122.6, 124.3, 124.9, 126.2, 127.3, 128.2, 129.7, 131.1, 135.1, 139.5, 152.1, 153.2, 160.4, 160.5. MS (EI): m/z=383 [M^+]. Anal. Calcd for $C_{23}H_{17}N_3SO$: C, 72.02; H, 4.47; N, 10.96. Found: C, 71.89; H, 4.45; N, 11.01.

*4.4.15. 2-[3-(4-Ethoxyphenyl)-1-phenyl-1H-pyrazole-4-yl]-1,3-benzoxazole (**8e**)*

Orange solid; mp 189–191 °C; R_f=0.44 (AcOEt/petroleum ether 50%). IR (KBr): 3430, 2930, 1631, 1583, 1450, 1240, 1045, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.43 (t, 3H, J=6.9 Hz, $-OCH_2CH_3$), 4.09 (q, 2H, J=6.9 Hz, $-OCH_2CH_3$), 6.98 (d, 2H, J=9.1 Hz, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.34 (t, 1H, J=7.6 Hz, Ar-H), 7.46–7.54 (m, 3H, Ar-H), 7.69 (d, 1H, J=6.9 Hz, Ar-H), 7.80 (d, 2H, J=7.6 Hz, Ar-H), 7.94 (d, 2H, J=8.4 Hz, Ar-H), 8.68 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.9, 63.6, 109.9, 110.4, 114.3, 119.4, 119.8, 124.5, 124.7, 127.4, 129.7, 130.2, 130.6, 139.4, 142.0, 147.0, 150.2, 152.1, 158.6, 159.7. MS (EI): m/z=381 [M^+]. Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.44; H, 5.11; N, 11.09.

*4.4.16. 2-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-1,3-benzoxazole (**8f**)*

Colorless solid; mp 205–207 °C; R_f=0.44 (AcOEt/petroleum ether 25%). IR (KBr): 3411, 1627, 1590, 1502, 1454, 1391, 1244, 1093, 989 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.32–7.33 (m, 2H, Ar-H), 7.37–7.39 (m, 1H, Ar-H), 7.45–7.53 (m, 5H, Ar-H), 7.71 (d, 1H, J=9.1 Hz, Ar-H), 7.81 (d, 2H, J=8.4 Hz, Ar-H), 7.99 (d, 2H, J=8.4 Hz, Ar-H), 8.71 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.3, 110.4, 119.5, 124.6, 124.9, 127.7, 128.5, 129.8, 130.3, 130.6, 134.9, 139.3, 141.9, 150.2, 151.1, 158.1. MS

(EI): m/z=372 [M^+], 374 [M^{+2}]. Anal. Calcd for $C_{22}H_{14}ClN_3O$: C, 71.07; H, 3.80; N, 11.30. Found: C, 71.25; H, 3.75; N, 11.25.

*4.4.17. 2-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-methyl-1,3-benzoxazole (**8g**)*

Colorless solid; mp 210–214 °C; R_f=0.52 (AcOEt/petroleum ether 30%). IR (KBr): 2920, 1589, 1500, 1262, 1223, 1057, 944, 830, 799 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.46 (s, 3H, $-CH_3$), 7.11 (d, 1H, J=8.4 Hz, Ar-H), 7.34–7.39 (m, 2H, Ar-H), 7.49–7.52 (m, 3H, Ar-H), 7.60 (d, 2H, J=8.4 Hz, Ar-H), 7.80 (d, 2H, J=7.6 Hz, Ar-H), 7.91 (d, 2H, J=8.4 Hz, Ar-H), 8.68 (s, 1H, pyrazolyl-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.6, 109.7, 110.4, 119.8, 123.3, 126.1, 127.7, 129.7, 130.9, 131.1, 131.4. MS (EI): m/z=430 [M^+], 432 [M^{+2}]. Anal. Calcd for $C_{23}H_{15}BrN_3O$: C, 64.20; H, 3.75; N, 9.77. Found: C, 64.25; H, 3.69; N, 10.02.

*4.4.18. 2-(1-Methyl-1H-indol-2-yl)-1,3-benzothiazole (**10a**)*

Colorless solid; mp 147–149 °C; R_f=0.66 (AcOEt/petroleum ether 30%). IR (KBr): 3419, 3051, 1542, 1450, 1345, 1310, 1191, 1150, 975, 787, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.31 (s, 3H, $-NCH_3$), 7.17–7.20 (m, 2H, Ar-H), 7.33–7.44 (m, 3H, Ar-H), 7.48–7.51 (m, 1H, Ar-H), 7.67 (d, 1H, J=8.4 Hz, Ar-H), 7.88 (d, 1H, J=7.6 Hz, Ar-H), 8.06 (d, 1H, J=8.4 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 32.4, 107.3, 110.2, 120.6, 121.4, 121.6, 123.3, 124.2, 125.4, 126.4, 127.3, 132.3, 134.5, 139.8, 154.3. 160.7. MS (EI): m/z=264 [M^+]. Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.81; H, 4.62; N, 10.53.

*4.4.19. 2-(1-Methyl-1H-indol-2-yl)-1,3-benzoxazole (**10b**)*

Colorless solid; mp 161–163 °C; R_f=0.55 (AcOEt/petroleum ether 25%). IR (KBr): 2332, 1579, 1450, 1340, 1240, 1141, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.31 (s, 3H, $-NCH_3$), 7.18 (t, 1H, J=7.6 Hz, Ar-H), 7.35–7.38 (m, 3H, Ar-H), 7.42 (d, 2H, J=10.7 Hz, Ar-H), 7.57 (d, 1H, J=7.6 Hz, Ar-H), 7.72 (d, 1H, J=7.6 Hz, Ar-H), 7.80–780 (m, 1H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 32.2, 107.6, 110.2, 110.5, 119.9, 120.7, 122.1, 124.5, 124.6, 125.2, 126.3, 126.9, 139.9, 142.2, 149.9, 157.8. MS (EI): m/z=248 [M^+]. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.55; H, 4.75; N, 11.39.

*4.4.20. 2-(1H-Pyrrol-2-yl)-1,3-benzoxazole (**10c**)*

Pink solid; mp 144–146 °C; R_f=0.51 (AcOEt/petroleum ether 30%). IR (KBr): 3401, 1629, 1585, 1455, 1403, 1243, 1117, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.36–6.38 (m, 1H, Ar-H), 7.04–7.05 (m, 1H, Ar-H), 7.28–7.33 (m, 2H, Ar-H), 7.52 (d, 1H, J=7.6 Hz, Ar-H), 7.64 (d, 1H, J=7.6 Hz, Ar-H), 10.25 (s, 1H, $-NH$). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.5, 110.9, 113.3, 118.9, 119.9, 123.1, 124.4, 124.7, 150.2, 158.2, 163.7. MS (EI): m/z=184 [M^+]. Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.81; H, 4.25; N, 15.25.

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