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PAPER

Ru/C: A Simple heterogeneous catalyst for the amination of azoles under ligand free conditions

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A ligand free Ru/C-catalyzed amination of 2-halo azoles with a broad scope of aminating reagents has been developed. Utilizing this protocol a variety of 2-aminoazole derivatives were synthesized in moderate to good yields. The methodology is operationally simple and not sensitive to air as well as moisture and it provides potentially useful products by using inexpensive and recyclable catalytic system under ligand free conditions, without significant loss of its catalytic activity up to four cycles.

Introduction

The discovery of mild and versatile methods for the formation of C-N bond via cross-coupling reaction as the most powerful tool to synthesize pharmacologically active products represents potential research domain. Aromatic nitrogen heterocyclic derivatives are ubiquitous structural motifs appearing in numerous biologically interesting natural products, as well as compounds of agrochemical and material sciences[1] continued research in C-N coupling reactions produced an array of interesting approaches including Ullmann coupling[2] and Buchwald−Hartwig reactions.[3]

In recent years, synthesis of 2-aminoazoles has gained much attention in synthetic organic chemistry as functionalized azoles are valuable structural scaffolds[4] and show great potential in the development of novel therapeutics.[5, 6] For example, Riluzole(**1**) is employed in the treatment of amyotrophic lateral sclerosis.[7] 5-HT receptors (**2**) (5-HT=5-hydroxytryptamine, seretonine) are targets for the treatment of Alzheimer's disease and schizophrenia.[8] R116010 (**3**) acts as an anticancer drug[9] and N- disubstituted 2-aminobenzothiazole (**4**) is used as anti-HIV agent[10](**Figure 1**).

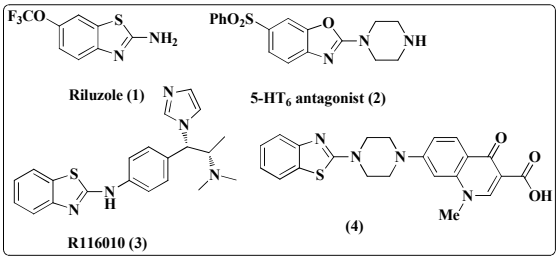

Figure 1. Some examples of bioactive 2-aminoazoles.

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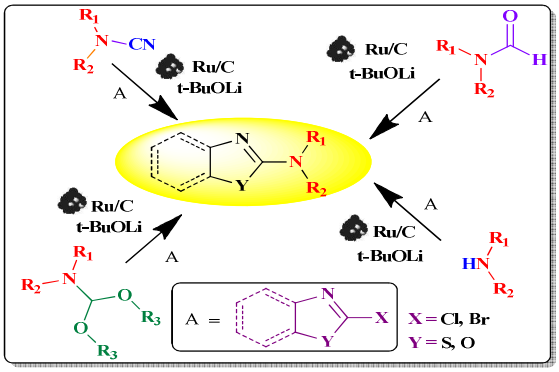
In view of the importance of 2-aminoazoles several procedures have been developed for the amination of azoles under the catalysis of transition metals, such as catalysts ofPd[11], Cu[12], Fe[13], Ni[14], Ag[15] and Sc[16] and their salts as well as metal free conditions.[17] However, these catalyst systems employed are usually not recyclable, expensive and moisture sensitive, thereby reducing the turn over number (TON) or turn over frequencies (TOF) which are significant from industrial point of view.

Recently our research group reported a green protocol for the synthesis of 2-N-substituted benzothiazoles by using nano copper oxide as a recyclable catalyst. [18]



Scheme 1. Ru/C catalyzed amination of 2- Chloro azoles.

Ru/C has emerged as an important heterogeneous catalyst in synthetic organic chemistry. However, only few reports are found in literature on charcoal-supported ruthenium catalysis. [19] To the best our knowledge, there is no research report on the amination of 2-haloazoles with formamides / cyanamides / N,N-DMF di-alkyl acetal / amines catalyzed by recyclable Ru/C. In continuation of our interest in the field of transition metal catalyzed cross-coupling reactions, [20] herein, we report recyclable Ru/C-catalytic system for the amination of readily available 2-haloazoles under the influence of aminating reagents ing LiOtBu as a base. (**Scheme 1**).

Results and Discussion

As a model reaction, initially the amination of 2-chloro benzothiazole (1.0 mmol) was investigated in DMF (2 ml) by using 5 wt % Ru/C (20 mg) under various conditions (Table 1). Among different bases examined KOH, Et_3N, Na_2CO_3, Cs_2CO_3, and K_3PO_4 decreased the yields (Table 1, Entries 1-5). Whereas other bases such as NaOtBu and KOtBu provided the desired cross coupling products in moderate yields (Table 1, Entries 6, 7) However with LiOtBu product was obtained in maximum yield (Table 1, entry 8). The control experiments revealed that in the absence of either catalyst or the base the reaction did not proceed (Table 1, entries 11-12). The reaction is also very sluggish at room temperature (Table 1, Entry 9). Nevertheless, high yield was obtained when the reaction was conducted at 80 ^{O}C. (Table 1, Entry 8). Increasing the reaction time to 12 h, did not improve the yield of the product (Table 1, entry 10). After screening several parameters, it was concluded that the desired cross-coupling product was formed in a high yield when 2-chlorobenzothiazole (1.0 mmol) was aminated in the presence of LiOtBu (1.0 mmol) and DMF (2 ml) when 5 wt % Ru/C (20 mg) catalyst was used at 80 ^{o}C.

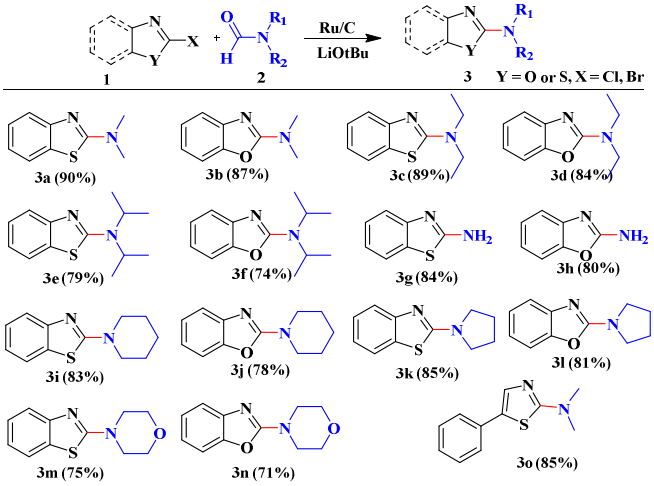
Table 1. Optimization studies: Screening of various bases.[a]

Entry	Base (equiv)	temp (°C)	time (h)	Yield [%][b]
1	KOH	80	8	28
2	Et_3N	80	8	19
3	Na_2CO_3	80	8	40
4	Cs_2CO_3	80	8	74
5	K_3PO_4	80	8	40
6	NaOtBu	80	8	51
7	KOtBu	80	8	62
8	**LiOtBu**	**80**	**8**	**90**
9	LiOtBu	rt	8	25
10	LiOtBu	80	12	93
11	LiOtBu	80	8	0[c]
12	-	80	8	0[d]

[a] Reactions were carried out with 2-chlorobenzothiazole (1.0 mmol), base (1.0 mmol), Ruthenium 5 Wt. % on Carbon (20 mg) and DMF (2 mL). [b] Isolated yield of the pure product. [c] Absence of catalyst. [d] Absence of base

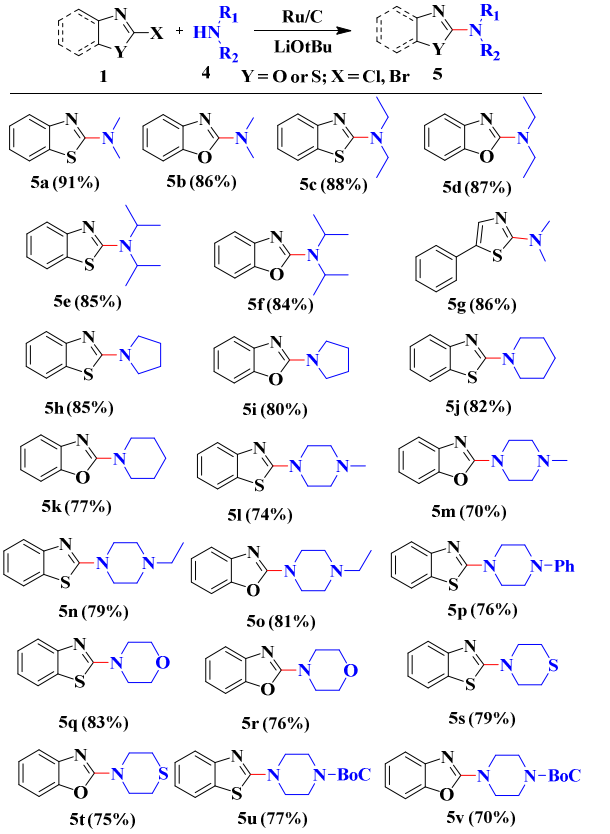
Under the optimized experimental conditions, the reaction of 2-halo benzothiazole and benzoxazole derivatives with different formamides produced the desired cross coupling products in good yields (Table 2). The reaction of 2-halo benzothiazole and benzoxazole with N,N-Dimethylformamide, N,N-Diethylformamide and N,N-di-tert-butylformamide gave the desired cross coupling products in excellent yields (Table 2, entries, **3a-3f**). Interestingly formamide reacted with 2- chloro benzothiazole and benzoxazole to give the corresponding coupling products in excellent yields (Table 2, entries, **3g**, **3h**). The formamide derivatives with piperidine, pyrrolidine and morpholine systems were reacted with 2-halo benzothiazole and benzoxazoles to obtain the corresponding 2-aminated azoles in high yields (Table 2, entries, **3i-3n**). 2-Bromo-4-phenylthiazole reacted with DMF to give the desired product in good yield (Table 2, entry, **3o**).

Table 2. Scope of the substates: various azoles and formamides.[a]



[a] Reaction conditions: Azole (1.0 mmol), LiOtBu (1.0 mmol), Ruthenium 5 Wt. % on Carbon (20 mg), formamides (2 mL) at 80 ^{O}C for 8h.

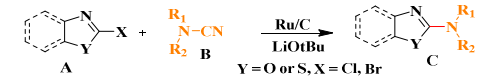
Table 3. Scope of the substrates: various azoles and amines.[a]

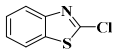
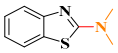
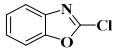
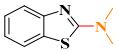
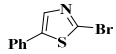
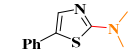
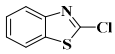
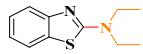
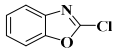
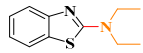
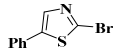
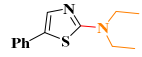
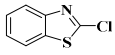
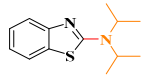
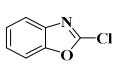
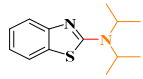


[a] Reaction conditions: Azole (1.0 mmol), LiOtBu (1.0 mmol), Ruthenium 5 Wt. % on Carbon (20 mg), amines (2 mL) at 80 ^{O}C for 8h.

Under similar reaction conditions, this methodology was observed to be compatible with a broad range of aliphatic and cyclic amines with both 2-halo benzothiazoles and benzoxazoles. Aliphatic acyclic amines such as dimethyl (**5a**, **5b**, **5g**), diethyl (**5c**, **5d**), and diisopropyl (**5e**, **5f**), amines underwent smooth conversion to the desired products with excellent yields. In addition, other cyclic secondary amines such as pyrrolidine (**5h**, **5i**), piperidine (**5j**, **5k**), 1-methylpiperazine (**5l**, **5m**), 1-ethylpiperazine (**5n**, **5o**), 1-phenylpiperazine (**5p**), morpholine (**5q**, **5r**), thiomorpholine (**5s**, 5**t**), 1-boc-piperazine(**5u**, **5v**), were also coupled with 2- halo benzothiazoles and benzoxazoles to obtain the corresponding 2-aminated azoles in good to excellent yields (Table 3).

Table 4. Scope of the substrates: various azoles and cyanamides.[a]



Entry	A	B	C	Yield [%][b]
1				90
2				84
3				87
4				86
5				79
6				81
7				83
8				78

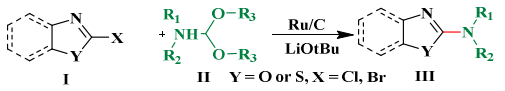
[a] Reaction conditions: Azole (1.0 mmol), LiOtBu (1.0 mmol), Ruthenium 5 Wt. % on carbon (20 mg), cyanamide (2 mL) at 80 °C for 8h. [b] Isolated yield of the pure product.

As shown in Table 4, several 2-halo azoles were successfully reacted with different cyanamides such as methyl, ethyl and isopropyl cyanamides to provide the corresponding products in moderate to good yields under the optimized experimental reaction conditions (Table 4, Entries 1–8).

In continuation of our interest, N,N-dimethylbenzo[d]azol-2-amines were also synthesized by reacting 2-haloazoles with different N,N-DMF di-alkyl acetal derivatives to obtain the expected products in good yields (Table 5).

After completion of the reaction, Ru/C catalyst was separated by centrifugation and washed with ethyl acetate followed by acetone, to dry in hot air oven. This dried Ru/C was reused directly for the next reaction cycle. No significant loss of catalytic activity was observed up to four cycles (**Figure 1**). This was confirmed by SEM analysis (**Figure 2**). A comparative SEM analysis study of the fresh catalyst and the recovered catalyst after four cycles confirmed that shape and size of the particles remain unchanged and this supports the assumption that the morphology of the catalyst remains the same even after recycling.

Table 5. Scope of the substrates: various azoles and N,N-DMF di-alkyl acetals.[a]



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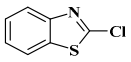
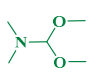
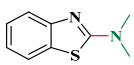
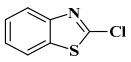
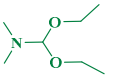
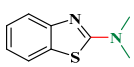
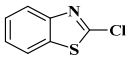
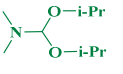
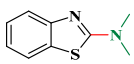
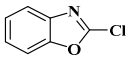
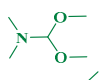
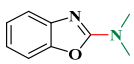
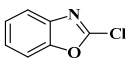
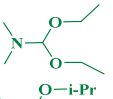
1				76
2				72
3				69
4				68
5				64
6				58
7				70
8				67
9				61

[a] Reaction conditions: azole (1.0 mmol), LiOtBu (1.0 mmol), Ruthenium 5 Wt. % on carbon (20 mg), N,N-DMF di-alkyl acetal (2 mL) at 80 °C for 8h. [b] Isolated yield of the pure product

Figure 1. Ru/C recyclability data

(a) **(b)**

Figure 2. Proposed SEM images of **(a)** native Ru/C **(b)** after four cycles Ru/C

Conclusions

In summary, we have demonstrated the efficiency of recyclable Ru/C as a catalyst in a novel protocol for the preparation of various substituted 2-aminated azoles via cross coupling of various 2-chloroazoles with formamides, amines, cyanamides and N,N-DMF di-alkyl acetals. This facile approach provides a green and practical methodology for the synthesis of 2-aminated azole derivatives. The recyclability and low cost of the catalyst system, compatibility of different amine sources, short reaction time, wide substrate scope and excellent product yields make this approach attractive.

Experimental Section

General Experimental Procedure for the amination of 2-chlorobenzothiazole: The reaction was carried in a 25 mL round bottom flask equipped with magnetic stir bar charged with 2-chlorobenzothiazole(1 mmol), aminating agent (2 mL), LiOtBu (1.0 mmol), and Ru/C (20 mg) catalyst. The resulting reaction mixture was stirred at 80 ^{O}C for 8h. The reaction progress was monitored by TLC. After the reaction, Ru/C was separated by centrifugation, the solvent was evaporated and the crude product was purified by column chromatography. The identity and purity of the product was confirmed by ^{1}H NMR, ^{13} C NMR and ESI-MS**.**

N,N-dimethylbenzo[d]thiazol-2-amine(3a):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.55 (m, 2H), 7.32-7.25 (m, 1H), 7.07-7.02 (m, 1H), 3.19 (s, 6H); ^{13}C NMR (75 MHz,$CDCl_3$):168.7, 153.2, 131.1, 130.0, 127.9, 125.9, 120.7, 118.7, 40.1. ESI- MS: *m/z* 179 [M+1].

N,N-dimethylbenzo[d]oxazol-2-amine(3b):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35(d, *J* =7.7Hz, 1H), 7.23 (d, *J* =7.9Hz, 1H), 7.15 - 7.12 (m, 1H), 7.0-6.97 (m, 1H), 3.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 148.9, 143.6, 123.8, 120.2, 115.9, 108.5, 37.6; ESI- MS: *m/z* 163 [M+1].

N,N-diethylbenzo[d]thiazol-2-amine(3c):^{1}H NMR (300 MHz, $CDCl_3$): δ7.53 (t, *J* = 8.6 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.01 – 6.96 (m, 1H), 3.48 – 3.42 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ166.8, 152.9,130.2, 125.3, 120.2, 120.1, 118.1, 44.9, 12.4; ESI- MS: *m/z* 207 [M+1].

N,N-diethylbenzo[d]oxazol-2-amine(3d):^{1}H NMR (300 MHz, $CDCl_3$): δ7.35 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 3.55 (q, *J* = 7.1 Hz, 5H), 1.25 (t, *J* = 7.1 Hz, 8H); ESI- MS: *m/z* 191[M+1**].**

N,N-diisopropylbenzo[d]oxazol-2-amine(3f):^{1}H NMR (300 MHz, $CDCl_3$): δ7.35 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 4.28 - 4.15 (m, 2H), 1.38 (d, J = 6.9 Hz, 12H);^{13}C NMR (75 MHz, $CDCl_3$): δ162.2, 148.4, 142.8, 123.5, 119.5, 115.4, 108.2, 47.5, 20.7; ESI- MS: *m/z* 219[M+1].

benzo[d]thiazol-2-amine(3g): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.93 Hz, 1H), 7.496 (d, *J* = 7.93 Hz, 1H), 7.32 - 7.26 (m, 1H), 7.14 - 7.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ166.6, 151.4, 130.9, 125.9, 122.1, 120.8, 118.6; ESI- MS: *m/z* 151[M+1].

2-(piperidin-1-yl)benzo[d]thiazole(3i): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 19.3, 7.9 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 3.59-3.58 (m, 4H), 1.68 (S, 6H); ^{13}C NMR (75 MHz, $CDCl_3$):δ168.8, 152.8, 125.7, 120.9, 120.4, 118.6, 49.5, 24.1, 25.2;ESI- MS: *m/z* 219[M+1].

2-(piperidin-1-yl)benzo[d]oxazole(3j):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 15.8, 7.5 Hz, 2H 2H), 7.22 (t,,*J* = 7.5 Hz, 1H) 7.03 - 6.96 (m, 1H), 3.59 - 3.51 (m, 4H), 1.69 (S, 6H);^{13}C NMR (75 MHz, $CDCl_3$): δ161.7, 148.2, 142.0, 123.9, 122.0, 120.4, 115.5, 109.8, 108.5, 46.5, 25.0, 23.7; ESI- MS: *m/z* 203[M+1].

2-(pyrrolidin-1-yl)benzo[d]thiazole(3k):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, J = 8.3, 4.9 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.06 – 7.02 (m, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.09 – 2.05 (m, 2H).; ESI- MS: *m/z* 205[M+1].

4-(benzo[d]thiazol-2-yl)morpholine(3m):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 -7.28 (m, 1H), 7.21 - 7.18 (m, 1H), 7.14 - 7.08 (m, 1H), 7.0 - 6.94 (m, 1H) 3.77 - 3.71 (m, 4H) 3.65 - 3.62 (m, 4H) ;^{13}C NMR (75 MHz, $CDCl_3$): δ168.9, 152.3, 126.0, 121.6, 120.7, 119.2,66.1,48.4;ESI- MS: *m/z* 221[M+1].

2-morpholinobenzo[d]oxazole(3n):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.32 - 7.28 (m, 1H), 7.12 - 7.07 (m, 1H),3.83 - 3.81 (m, 4H), 3.62 - 3.60(m, 4H);^{13}C NMR (75 MHz, $CDCl_3$): δ161.1, 148.1, 124.3 123.5, 121.2, 108.8, 116.0, 65.9, 45.7;ESI-MS: *m/z* 205[M+1].

N,N-dimethyl-5-phenylthiazol-2-amine(3o):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 7.5 Hz, 2H), 7.23 - 7.08 (m, 3H), 6.52(s, 1H), 2.90(s, 6H);^{13}C NMR (75 MHz, $CDCl_3$): δ151.8, 135.0, 128.2, 127.2, 125.8, 100.7, 39.8;ESI- MS: *m/z* 205[M+1].

2-(4-methylpiperazin-1-yl)benzo[d]oxazole(5m):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 - 7.47 (m, 2H), 7.27 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 3.63 (t, J = 4.9 Hz, 4H), 2.49 (t, J = 4.9 Hz, 4H), 2.31 (s, 3H); ESI- MS: *m/z* 286[M+1].

2-(4-ethylpiperazin-1-yl)benzo[d]thiazole(5n):^{1}H NMR (300 MHz, $CDCl_3$): δ7.60 - 7.54 (m, 2H), 7.29 (t, J = 7.7 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H),3.66 (t, J = 5.0 Hz, 4H), 2.57 (t, J = 4.6 Hz, 4H), 2.50 - 2.45 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ESI- MS: *m/z* 248 [M+1].

2-(4-phenylpiperazin-1-yl)benzo[d]thiazole(5p):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 - 7.29 (m, 1H), 7.27 - 7.18(m, 3H), 7.17 - 7.11(m, 1H), 7.01 - 6.83(m, 1H), 3.85 (t, J = 5.2 Hz, 4H), 3.28 (t, J = 5.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ161.8, 150.8, 148.6, 142.5, 129.2, 124.0, 120.9, 120.8, 116.9, 116.2, 108.7, 49.1, 45.5; ESI- MS: *m/z* 296[M+1].

tert-butyl4-(benzo[d]oxazol-2-yl)piperazine-1-carboxylate(5v):^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H),7.17 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 3.56 (d, *J* = 7.5 Hz, 8H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ161.7, 154.3, 148.5, 142.6, 123.9, 120.7, 116.2, 108.6, 80.1, 45.2, 28.1; ESI- MS: *m/z* 304 [M+1].

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