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A Cu $(NO_3)_2.3H_2O$ catalysed facile synthesis of substituted 4(3H)-quinazolinones and benzimidazoles

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Abstract. One pot synthesis of alkyl, aryl, heteroaryl mono(2)substituted 4(3H)-quinazolinones and 2-aryl or heteroaryl, 1-arylmethyl or heteroarylmethyl -1H-benzimidazoles using a water soluble Cu $(NO_3)_2.3H_2O$ catalyst at room/ambient temperature in excellent yield.

Keywords. Quinazolinones; benzimidazoles; Cu $(NO_3)_2.3H_2O$.

1. Introduction

Diverse pharmacological activities of the two heterocycles, quinazolinone and benzimidazole derivatives have been well-established through a number of research articles. Quinazoline-4(3H)-ones possess pharmacological activities[1–11] such as analgesic, antibacterial, anticonvulsant, antidiabetic, antitumour, phosphorylation inhibition and CNS depressant activity. Similarly, broad spectrum pharmacological activities of benzimidazole core, classified by medicinal chemists as a 'privileged sub-structure' for drug design, possess affinity towards a variety of enzymes and protein receptors.[12] Benzimidazole containing structures exhibit significant activity against viruses such as HIV, herpes (HSV-1), influenza and human cytomegalovirus (HCMV).[13–17] Benzimidazole derivatives can also be used as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotension II inhibitors, 5-HT_3 antagonists in isolated guinea pig ileum, smooth muscle cell proliferation inhibitors, potential antitumour agents, antimicrobial agents and in diverse area of chemistry.[18–23] In addition, the treatment potency of benzimidazoles in diseases such as ischemia-reperfusion injury, hypertension and obesity have been reported recently.[24–26]

Several synthetic routes have been suggested for both 1,2 disubstituted-1H-benzimidazole[27–33] and 4(3H)-quinazolinone[34–37] derivatives. Widely used synthetic strategies for the preparation of 1H-1,2-benzimidazoles are the condensation of orthophenylenediamines and carboxylic acids (or its derivatives like nitriles, imidates and orthoesters) under vigorous dehydrating conditions,[38] rhodium catalysed hydroformylation reaction of *N*-alkenyl phenylenediamines,[39] reductive cyclisation reaction of *o*-nitroaniline with aldehydes,[40] palladium catalysed tandem carbonylation–cyclisation reaction of *o*-phenylenediamine,[31] palladium catalysed tandem dehydration-coupling reaction of 2-bromoaniline,[41] and solid phase supported synthesis.[42] Most of the methods suggested having limitations such as low yield, tedious work-up procedures, by-product formation, long reaction time, expensive reagents and lack of selectivity. In addition to that, some methods do not satisfy the requirements such as operational simplicity, economic viability, greater selectivity, ease of recovery of the products from the reaction mixture. However, condensation–aromatization reaction of orthophenylenediamine and aldehydes under oxidative conditions turned out to be the effective method to synthesize mono and di substituted benzimidazoles.[43,44] We have explored the catalytic efficiency of L- proline[45] in chloroform and Zn-proline complex[46] in water towards the synthesis of 1,2-disubstituted benzimidazoles at ambient temperature.

2. Experimental

All reagents and solvents available commercially were used without further purification. Reactions were followed by TLC analysis. Melting points were observed

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Table 1. Synthesis of 1,2 disubstituted-1H-benzimidazoles by the reaction of aliphatic, aromatic and hetero aromatic aldehydes with orthophenylenediamine, catalysed by $Cu(NO_3)_2.3H_2O$ in CH_3CN at room temperature.

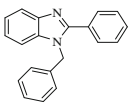
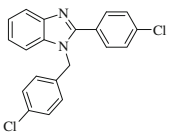
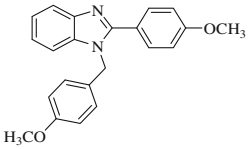
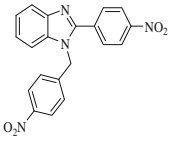
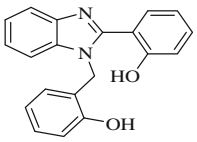
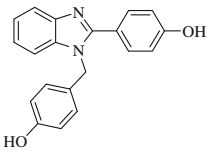
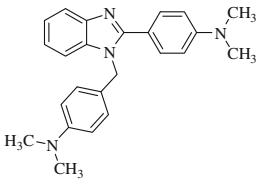
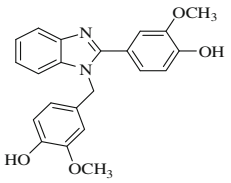
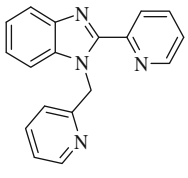
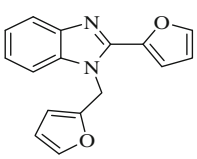
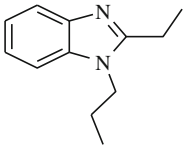
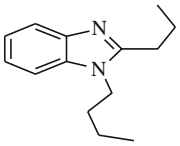
Entry	Aldehyde	Product	Stirring time (h)	Yield(%)*
1a	Benzaldehyde		5	92
1b	4-Chlorobenzaldehyde		8	75
1c	4-Methoxybenzaldehyde		5	82
1d	4-Nitrobenzaldehyde		8	70
1e	2-Hydroxybenzaldehyde		5	75
1f	4-Hydroxybenzaldehyde		5	70
1g	4-N,N-dimethyl amino benzaldehyde		6	78
1h	3-Methoxy -4-hydroxy benzaldehyde		6	72
1i	Pyridine-2-carboxaldehyde		10	75
1j	2-Furfural		5	80

Table 1. (*continued*).

Entry	Aldehyde	Product	Stirring time (h)	Yield(%)*
1k	Propanaldehyde		5	80
1l	*n*-Butyraldehyde		5	77

*Isolated yield.

using open capillaries in a sulphuric acid bath. IR and ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 as a solvent were recorded on Perkin-Elmer and Varian 300 MHz spectrometer, respectively.

2.1 *General procedure for synthesis of benzimidazoles and quinazolinones*

2.1a *Benzimidazoles*: A mixture of orthophenylenediamine (1 mmol), $Cu(NO_3)_2.3H_2O$ (20 mmol) and the appropriate aldehyde (2.3 mmol) in CH_3CN (10 mL) was stirred at room temperature for the time specified in table 1. Completion of the reaction was monitored by TLC. The product was washed with water and extracted with solvent ether. The product was purified by silica gel packed column chromatography eluted with ethylacetate/*n*-hexane (3:7) solvent system.

2.1b *Quinazolinones*: A mixture of anthranilamide (1 mmol), $Cu(NO_3)_2.3H_2O$ (20 mmol) and the appropriate aldehyde (1.3 mmol) in CH_3CN (10 mL) was heated at 80°C for the time specified in table 2. Completion of the reaction was monitored by TLC. The product was washed with water and extracted with ethyl acetate. The product was purified by silica gel packed column chromatography eluted with ethylacetate/*n*-hexane (3:7) solvent system.

2.2 *Spectral data of the compounds*

1a. IR spectrum,ν, cm^{-1}: 3030, 2926, 1468, 1328, 1444. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 5.45 (s, 2H,), 7.12 (dd, 2H, J = 8.2 Hz), 7.15–7.38 (m, 6H), 7.4–7.48 (m, 3H), 7.70 (dd, 2H, J = 8.2 Hz), 7.85 (d, 1H, J = 8 Hz).

1b. IR spectrum,ν, cm^{-1}: 2923, 2851, 1448, 1428, 1275, 744. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 5.39 (s, 2H), 7.59–7.61 (m, 2H), 7.60 (d, 2H, J = 8.6 Hz), 7.19 (d, 1H J = 7.7 Hz), 7.24–7.38 (m, 4H), 7.40–7.45 (m, 2H), 7.84 (d, 1H, J = 7.7 Hz).

1c. IR spectrum,ν, cm^{-1}: 3053, 2963, 2935, 1459, 1294, 1382, 1459. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz):3.77 (s,3H), 3.83 (s, 3H), 5.45 (s, 2H), 6.81 (d, 2H, J = 8 Hz), 6.99 (m, 4H), 7.22 (m, 3H), 7.64 (d, 2H, J = 9 Hz), 7.78 (d, 1H, J = 8 Hz).

1d. IR spectrum,ν, cm^{-1}: 3046, 2965, 1463, 1326, 1479. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 5.74 (s, 2H),7.19 (dd, 1H, J = 8 Hz), 7.23–7.32 (d, 2H, J = 9 Hz), 7.35 (td, 1H, J = 9 Hz), 7.54 (td, 1H, J = 7 Hz), 7.79 (d, 2H, J = 9 Hz), 7.91–7.98 (dd, 1H, J = 8 Hz), 8.15–8.2 (d, 2H, J = 8 Hz), 8.34 (d, 2H, J = 9 Hz).

1e. IR spectrum,ν, cm^{-1}: 3288, 3048, 2926, 1394, 1240, 1454, 1592. ^{1}H NMR spectrum, (300 MHz, $CDCl_3$ + DMSO), δ, ppm (J, Hz): 5.57 (s, 2H), 6.85–7.01 (m, 4H), 7.19–7.36 (m, 5H), 7.70–7.80 (m, 2H), 7.92 (d, 1H, J = 7.6 Hz), 2.52 (br s, 2H).

1f. IR spectrum,ν, cm^{-1}: 3246, 2923, 1515, 1443, 1246, 1347. ^{1}H NMR spectrum, (300 MHz, DMSO), δ, ppm (J, Hz): 5.35 (s,2H), 6.80–6.91 (m, 4H), 7.11–7.46 (m, 6H), 7.91 (d, 2H, J = 7.6 Hz), 10.86 (br.s, 2H).

1g. IR spectrum,ν, cm^{-1}: 2880, 2800, 1441, 1250, 1526. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm

Table 2. Synthesis of mono(2)-substituted 4(3H)-quinazolinones by the reaction of aliphatic, aromatic and hetero aromatic aldehydes with anthranilamide, catalysed by $Cu(NO_3)_2.3H_2O$ in CH_3CN at 80°C.

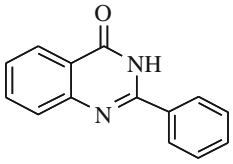
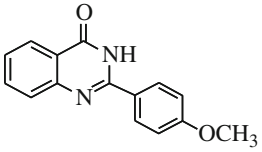
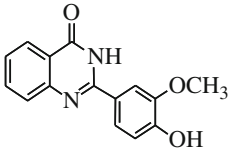
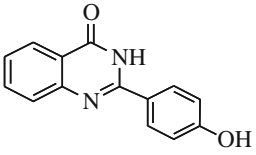
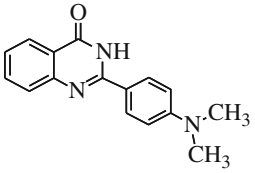
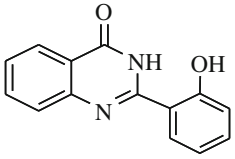
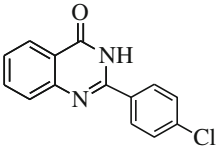
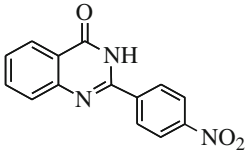
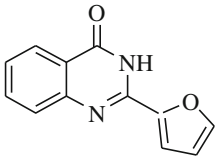
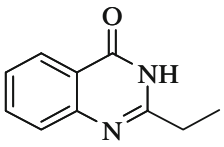
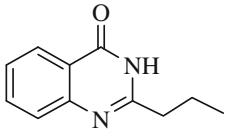
Entry	Aldehyde	Product	Heating time (h)	Yield (%)*
2a	Benzaldehyde		9	93
2b	4-Methoxybenzaldehyde		9.5	88
2c	3-Methoxy-4-hydroxy benzaldehyde		10	80
2d	4-Hydroxybenzaldehyde		10	75
2e	4-N,N-dimethylamino benzaldehyde		10	78
2f	2-Hydroxybenzaldehyde		11	84
2g	4-Chlorobenzaldehyde		10	79
2h	4-Nitrobenzaldehyde		12	78
2i	2-Furfural		10	77

Table 2. (*continued*).

Entry	Aldehyde	Product	Heating time (h)	Yield (%)*
2j	Propanaldehyde		10	80
2k	*n*-Butyraldehyde		10	77

*Isolated yield.

(J, Hz): 2.93 (s, 6H), 3.01(s, 6H), 5.37 (s, 2H), 6.66–6.75 (m, 4H), 6.95–7.02 (m, 2H), 7.14–7.29 (m, 2H), 7.63 (d, 2H, J = 8.8 Hz), 7.79 (m, 2H).

1h. IR spectrum,ν, cm^{-1}: 3399, 2998, 2935, 2832, 1458, 1274, 1389, 1458. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 3.70 (s, 3H), 3.81 (s, 3H), 5.39 (s, 2H), 6.49 (d, 1H, J = 7.9 Hz), 6.60 (d, 1H, J = 8.1 Hz), 6.90 (d, 2H, J = 8.4 Hz), 7.10–7.30 (m, 5H), 7.69 (d, 1H, J = 8.6 Hz), 8.40 (s, 1H), 8.95 (s, 1H).

1i. IR spectrum,ν, cm^{-1}: 3041, 2924, 2855, 1482, 1276, 1423. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 5.50 (s, 2H), 7.19–7.42 (m, 3H), 7.85 (d, 1H, J = 7.3 Hz), 7.98 (d, 1H, J = 7.8 Hz), 8.59 (d, 2H, J = 7.9 Hz), 8.58–8.62 (m, 3H), 8.72 (d, 1H, J = 8.1 Hz), 8.85 (s, 1H).

1j. IR spectrum,ν, cm^{-1}: 3114, 2926, 1506, 1254, 1216, 1452. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 5.69 (s, 2H), 6.20 (d, 1H, J = 7.8 Hz), 6.30 (d, 1H, J = 7.6 Hz), 6.61–6.79 (m, 1H), 7.23–7.41 (m, 4H), 7.34 (d, 1H, J = 7.4 Hz), 7.67–7.80 (m, 2H).

1k. IR spectrum,ν, cm^{-1}: 3104, 2906, 1526, 1224, 1442, 951. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.56 (t, 3H, J = 4.7 Hz), 1.09 (t, 3H, J = 4.1 Hz), 1.29 (m, 2H), 2.3 (q, 2H, J = 3.9 Hz), 4.7 (t, 2H, J = 4.3 Hz), 7.3 (d, 1H, J = 7.6 Hz), 7.6 (m, 3H).

1l. IR spectrum,ν, cm^{-1}: 3012, 2917, 1496, 1184, 1402, 935. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.81 (t, 3H, J = 4.2 Hz), 1.1 (t, 3H, J = 4.7 Hz), 1.5–1.9 (m, 6H), 2.1 (t, 2H, J = 4.9 Hz), 5.1 (t, 2H, J = 5.6 Hz), 7.1 (m, 4H).

2a. IR spectrum,ν, cm^{-1}: 1673, 1456, 1175,1342, 1030, 955, 730. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 7.56–7.62 (m, 4H), 7.75–7.84 (m,2H), 8.18–8.53 (m,3H), 12.46 (s, 1H).

2b. IR spectrum,ν, cm^{-1}: 1675, 1585, 1485, 1295, 1011, 870, 780. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 3.85 (s, 3H), 6.93–7.73 (m, 4H), 7.81 (d, 2H, J = 7.1 Hz), 8.13 (d, 2H, J = 7.3 Hz), 12.47 (s, 1H).

2c. IR spectrum,ν, cm^{-1}: 1668, 1578, 1493, 1288, 1143, 1027, 860, 770. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz):3.90 (s, 3H), 6.93–7.52 (m, 4H), 7.71 (d, 1H, J = 7.5 Hz) 7.75 (s, 1H) 7.82 (d, 1H, J = 7.2 Hz) 8.82 (s, 1H), 12.42 (s,1H).

2d. IR spectrum,ν, cm^{-1}: 1665, 1604, 1520, 1350, 1315, 960, 765. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 6.91 (m, 4H), 7.48 (d, 2H, J = 7.8 Hz), 7.68 (d, 2H, J = 7.7 Hz), 9.24 (s, 1H), 12.02 (s, 1H).

2e. IR spectrum,ν, cm^{-1}: 1668, 1601, 1524, 1450, 1295, 961, 764. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 3.04(s, 6H), 6.84 (m, 4H,), 7.44 (d, 2H, J = 7 Hz), 7.81 (d, 2H, J = 7.2 Hz), 12.04 (s, 1H).

2f. IR spectrum,ν, cm^{-1}: 1663, 1553, 1457, 1288, 1248, 948, 753 cm^{-1}. ^{1}H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): δ 6.73 (m, 4H), 7.49 (m, 4H), 9.24 (s, 1H), 12.34 (s, 1H).

2g. IR spectrum,ν, cm^{-1}: 1679, 1609, 1490, 1160, 1020, 950,735. ^1H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 7.52 (m, 4H), 7.76 (d, 2H, J = 6.6 Hz), 7.79 (d, 2H, J = 7.1 Hz), 11.80 (s, 1H).

2h. IR spectrum,ν, cm^{-1}: 1665, 1604, 1520, 1350, 948, 765, 638. ^1H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 7.43 (m, 4H) 7.48 (d, 2H, J = 7.6 Hz), 7.68 (d, 2H, J = 7.4 Hz), 12.02 (s, 1H).

2i. IR spectrum,ν, cm^{-1}: 1662, 1602, 1572, 1465, 1355, 1109, 707. ^1H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz):7.59 (m, 4H), 8.37(m, 3H), 11.39(s, 1H).

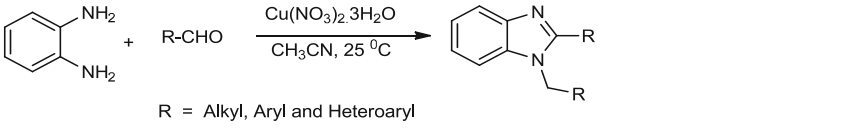
2j. IR spectrum,ν, cm^{-1}: 1680, 1450, 1295, 1200, 1137, 954, 771. ^1H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz):1.34(t, 3H, J = 9.4 Hz), 2.62(q, 2H, J = 5.8 Hz), 7.42 (m, 4H), 11.40 (s, 1H).

2k. IR spectrum,ν, cm^{-1}: 1680, 1450, 1295,1208, 958,771. ^1H NMR spectrum (300 MHz, DMSO), δ, ppm (J, Hz): 1.09 (t, 3H, J = 8.7 Hz), 1.83(m, 2H), 2.62(t, 2H, J = 6.2 Hz), 7.42 (m, 4H), 12.04 (s, 1H).

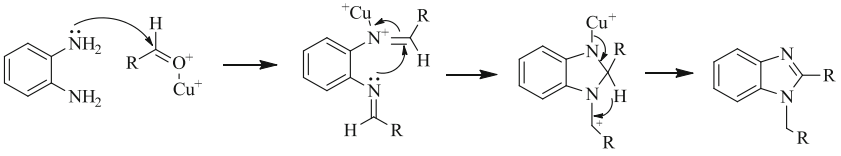
3. Results and discussion

In our attempt to find a water soluble, economical catalyst with activity at room temperature/ambient temperature, having good selectivity and yield. The efficiency of $Cu(NO_3)_2.3H_2O$ as a catalyst to synthesize 1,2 disubstituted benzimidazoles as well as mono(2)substituted 4(3H)-quinazolinones is reported here. Variety of catalytic substances like $AlCl_3$, $FeSO_4$, $Cu(OAC)_2$, $AgNO_3$, $Nd(NO_3)_2.6H_2O$, $Zn(NO_3)_2.6H_2O$, $Ni(NO_3)_2.6H_2O$, $CoCl_2$, $Ru(acac)_2$, $Ba(NO_3)_2$, $Al(NO_3)_3$, $ZnCl_2$, $CuSO_4.5H_2O$ in combination with different solvents such as DCM, DMF, THF, MIBK (methyl isobutyl ketone) were analysed for their catalytic activity. No reaction or very low yield (<10%) was observed.

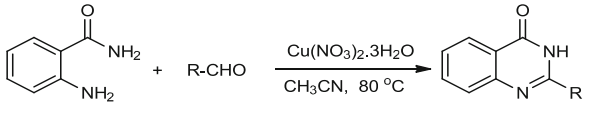
As shown in the scheme 1, 2-aryl-1-arylmethyl-1H-benzimidazoles were synthesized in high yields at room temperature. The results are summarized in table 1. We have examined the catalytic efficiency of $Cu(NO_3)_2.3H_2O$ towards anthranilamide and benzaldehyde reaction mixture at ambient temperature, 80°C afforded selectively 2-substituted quinazolinones with excellent yield (93%). The reaction procedure was extended to other aryl, heteroaryl and aliphatic aldehydes to observe the versatility of the catalyst also resulted



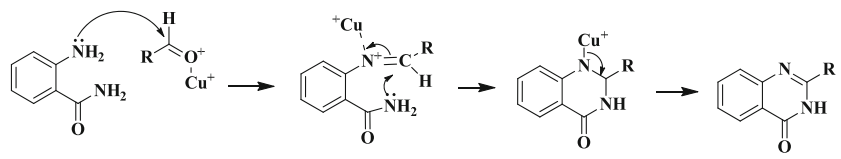
Proposed mechanism for scheme 1



Scheme 1. Synthesis of benzimidazoles.



Proposed mechanism for scheme 2



Scheme 2. Synthesis of 4(3H)-quinazolinones.

in good to excellent yield. Various methods are reported in the literature for the synthesis of mono(2)substituted quinazolinones through the condensation of isatoic anhydride and orthoester with ammonium acetate catalysed by silica-sulphuric acid,[47] antranilamide and orthoester catalysed by $AlCl_3$–SiO_2,[48] isatoic anhydride and aryl aldehydes with ammonium acetate catalysed by I_2-acetic acid,[49] anthranilamide with aldehyde using $NaHSO_3$,[50] DDQ[51] and $CuCl_2$.[52] We observed that the selective synthesis of mono(2)substituted quinazolinones catalysed by $Cu(NO_3)_2.3H_2O$ (scheme 2) in the present study seem to be good with excellent yield compared to the previous reports. The results are summarized in table 2. The structures of the compounds synthesized were characterized by spectral techniques (IR and ^{1}H NMR) and comparison of melting points with authentic samples.

4. Conclusion

An efficient and versatile method has been achieved for the synthesis of 2-aryl-1-arylmethyl, 2-heteroaryl-1-heteroarylmethyl-1H-benzimidazoles and 2-alkyl, 2-aryl, 2-heteroaryl quinazolin-4(3H)-ones via $Cu(NO_3)_2.3H_2O$ catalysed cyclization-oxidative coupling of orthophenylene diamine with aldehydes and anthranilamide with aldehydes, respectively in one pot with excellent yield.

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