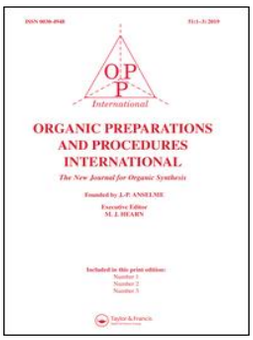

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EXPERIMENTAL PAPER

Nanoparticle-Promoted Synthesis of Trisubstituted Imidazoles in a Green Medium

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The imidazole ring system is one of the most important heterocyclic substructures and has been found in a large number of pharmacologically active compounds, including the fungicide ketoconazole,[1] the proton pump inhibitor omeprazole,[2] the antiulcerative cimetidine,[3] and the hypnotic agent etomidate.[4] In addition, imidazoles occur in common scaffolds of highly significant biomolecules, including biotin, the critical amino acid histidine, histamine, the pilocarpine alkaloids[5] and such dipeptides as carnosine and anserine.[6] Imidazoles have been used in polymers,[7] fluorescent materials,[8] ionic solvents,[9] in N-heterocyclic carbene chemistry[10] and in photography as photosensitive compounds.[11] In particular, many of the 2,4,5-trisubstituted imidazoles are known as fungicides,[12] herbicides,[12] plant-growth regulators,[13] therapeutic agents,[1] inhibitors of P38MAP kinase,[14] antibacterials[15] and anticonvulsants.[16] 2,4,5-Trisubstituted imidazoles have been prepared by the reaction of aryl nitriles and α,α-dilithioarylnitromethanes[17] or by multistep synthesis.[18] 2,4,5-Trisubstituted imidazoles are often synthesized via the three component cyclocondensation of a 1,2-diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde and ammonium acetate in the presence of a catalyst. The catalysts have included zeolite HY/silica gel,[19] $ZrCl_4$,[20] $NiCl_2{\cdot}6H_2O$,[21] ionic liquids,[22] iodine,[23] sodium bisulfite,[24] acidic Al_2O_3,[25] AcOH,[26] NH_4OAc, $Yb(OTf)_3$,[27] Fe_3O_4-PEG-Cu[28] and $CuFe_2O_4$.[29] Each of these methods has its own advantages and disadvantages, but a simple and efficient procedure for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from readily accessible starting materials would be a worthy advance. In this context, polyethylene glycols (PEGs) are eco-friendly solvents and offer important solvent characteristics. [30,31] Recently, a catalyst made up of copper nanoparticles on charcoal (Cu/C) has been reported as an excellent heterogeneous catalyst for the synthesis of triazoles,[32] propargylamines,[33] benzimidazoles[34] and 2-amino-3-cyanopyridine derivatives.[34] As part of our ongoing studies in the preparation of novel compounds,[32–45] we now wish to report a simple and efficient method for the synthesis of 2,4,5-triaryl substituted imidazoles in the presence of Cu/C using readily available starting materials in PEG 200 as a green solvent.

The Cu/C catalyst was synthesized according to our previously published procedures.[32,33] The catalytic performance of the Cu/C nanoparticles was tested in the condensation reaction among benzil (1 mmol), benzaldehyde (1 mmol) and ammonium

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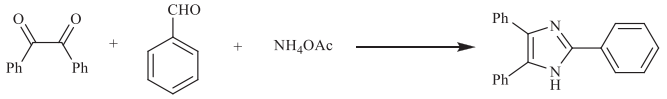
Table 1. Synthesis of 2,4,5-triphenyl imidazole using Cu/C under different conditions.[a]



Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	H_2O	Cu/C (1)	100	6.5	8
2	$CHCl_3$	Cu/C (1)	reflux	7	32
3	THF	Cu/C (1)	reflux	6.5	32
4	Toluene	Cu/C (1)	100	6	74
5	2-Ethylhexanol	Cu/C (1)	100	6	67
6	Dimethyl formamide	Cu/C (1)	100	6.5	48
7	Dimethyl sulfoxide	Cu/C (1)	100	6.5	53
8	–	Cu/C (1)	100	7.5	44
9	MeOH	Cu/C (1)	reflux	7	85
10	EtOH	Cu/C (1)	reflux	7	87
11	PEG 200	Cu/C (1)	100	1.5	93
12	PEG 200	Cu/C (1)	R.T	6	0
13	PEG 200	Cu/C (1)	70	7	45
14	PEG 200	Cu/C(0.5)	100	1.5	78
15	PEG 200	Cu/C(2)	100	1.5	95
16	PEG 200	–	100	7.5	NR
17	PEG 200	Active charcoal	100	1.5	43
18	PEG 200	$CuSO_4$	100	1.5	57
19	PEG 200	$Cu(OAC)_2$	100	1.5	69
20	PEG 200	CuI	100	1.5	53

[a]Reaction conditions: benzil (1mmol), benzaldehyde (1 mmol), ammonium acetate (4 mmol) and Cu/C (1 mol%) in PEG 200 (2 mL).
[b]Isolated yields.

acetate (4 mmol) as a model. The results of the optimization study for the multicomponent synthesis of 2,4,5-triphenyl imidazoles are summarized in Table 1.

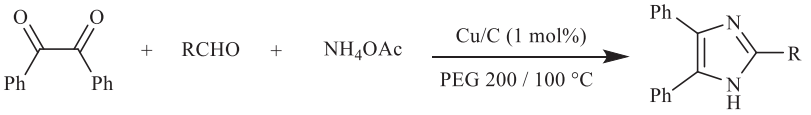
It was found that using PEG 200 in this reaction gave the best yield of product (93%) at 100 °C in comparatively short reaction times (Table 1, entry 11). Lower temperatures or other solvents led to lower yields. The outcome seems to reflect a delicate balance among the polarity of the solvent, its ability to solubilize the reagents and the stabilization of putative reactive intermediates. The optimized conditions were determined as: benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (4 mmol) in the presence of Cu/C (1 mol%) in PEG 200 at 100 °C to afford the desired product in 93% yield (Table 1, entry 11).

We then studied the general applicability of the catalyst for several derivatives of 2-aryl-4,5-diphenyl -1*H*-imidazoles (Table 2, entries 1-14).

A wide range of aromatic aldehydes bearing electron-donating and electron-withdrawing substituents underwent this one-pot, three-component cyclocondensation to furnish 2,4,5-trisubstituted imidazoles in high yields. The results indicated that the electronic and steric properties of the aldehyde had little impact on the efficiency of this reaction. After completion of reaction, the catalyst was recycled and directly used for another cycle. We found that the yields were consistently good through four cycles, and yields declined only in the fifth cycle and beyond.

Summing up, we found a simple and efficient one-pot strategy for the synthesis of 2,4,5-trisubstituted imidazoles from benzil, aldehyde and ammonium acetate, using inexpensive Cu/C nanocatalyst. In this procedure, PEG 200 is used as an eco-friendly

Table 2. Cu/C NPs catalyzed synthesis of 2,4,5-trisubstituted imidazole derivatives.[a]



Entry	Products	Time (h)	Yield (%)[b]
1	R = Ph **1**	1.5	93
2	R = 4-MePh **2**	2	88
3	R = 4-OmePh **3**	3	91
4	R = 4-ClPh **4**	2	92
5	R = 2,4-Cl_2Ph **5**	3	91
6	R = 2,6-Cl_2Ph **6**	3	90
7	R = 4-OHPh **7**	2	88
8	R = 3,4-OMe_2Ph **8**	2	84
9	R = 3-OMe,4-OHPh **9**	3	87
10	R = 2-styryl **10**	2	90
11	R = 4-N,N-dimethylPh **11**	3	87
12	R = anthracen-10-yl **12**	6	76
13	R = 4-CNPh **13**	2	89
14	R = furan-2-yl **14**	2	91

[a]Reaction conditions: benzil (1mmol), aldehyde (1 mmol), ammonium acetate (4 mmol) and Cu/C (1 mol%) in PEG 200 (2 mL).
[b]Isolated yields.

solvent. This method offers short reaction times, high yields, and catalyst reusability. It is hoped that this convenient method will further stimulate research on the title compounds.

Experimental section

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H-NMR at 250 MHz and ^{13}C NMR at 62.5 MHz) and Bruker Avance DPX-300 (^{1}H-NMR at 300 MHz and ^{13}C NMR at 75 MHz) spectrometer in pure deuterated solvents with TMS as an internal standard. Infrared (IR) spectra were obtained using a Shimadzu FTIR 8300 spectrophotometer. Elemental analyses were performed with a Thermo Finnigan CHNS-O 1112 series analyzer. Melting points were determined in open capillary tubes in a Büchi 535 circulating oil melting point apparatus and are uncorrected. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates, using *n*-hexane:ethyl acetate (5:1) as solvent. Column chromatography was carried out on short columns of silica gel 60 (70-230 mesh) in glass columns (2-3 cm diameter) using 15-30 g of silica gel per gram of crude mixture, with *n*-hexane:ethyl acetate (5:1) as solvent. Chemical materials were purchased from Fluka, Aldrich and Merck. The activated carbon was also purchased from Merck (Art. No. 9631, 0.3-0.05 mm).

General method for the synthesis of 2,4,5-trisubstituted imidazoles

Benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (4 mmol) and Cu/C (1 mol%) were stirred in PEG 200 (2 mL) at 100 °C for an appropriate time specified in Table 2. The reaction was monitored with TLC. When the reaction was completed, the mixture

was cooled down to room temperature and the catalyst was recovered by filtration.[32] Next, EtOAc (10 mL) was added to the reaction mixture. The organic layer was separated and then concentrated by vaporizing the solvent under reduced pressure. The resulting crude product was purified by recrystallization from ethyl acetate:n-hexane (1:2) or by column chromatography using *n*-hexane:ethyl acetate (5:1) as an eluent to give pure 2,4,5-trisubstituted-1*H*-imidazoles in the yields specified.

2,4,5-Triphenyl-1H-imidazole (1)

White crystals (93%), mp: 277-279 °C. IR (KBr, cm^{-1}): 3448 (b), 3058 (w), 3011 (w), 2842 (w), 1640 (m), 1500 (s), 1463 (s), 1146 (m), 1084 (m), 998 (m), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.22-7.33 (m, 3H), 7.36 (d, 2H, J = 6.9 Hz), 7.43-7.51 (m, 8H), 8.06 (d, 2H, J = 7.5 Hz), 12.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 125.6, 126.9, 127.5, 128.2, 128.7, 128.9, 129.2, 130.8, 131.6, 135.6, 137.5, 145.9.

Anal. Calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44. Found: C, 84.97; H, 5.31.

4,5-Diphenyl-2-p-tolyl-1H-imidazole (2)

White crystals (88%), mp: 238-240 °C. IR (KBr, cm^{-1}): 3417 (b), 3033 (w), 2975 (w), 2866 (w), 1621 (m), 1515 (s), 1478 (m), 1382 (w), 1161 (m), 1000 (s), 836 (m), 768 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.33 (s, 3H), 7.26 (d, 4H, J = 7.8 Hz), 7.41-7.49 (m, 8H), 7.95 (d, 2H, J = 7.5 Hz), 12.58 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4, 125.6, 127.5, 128.1, 128.9, 129.7, 131.6, 138.2, 146.1.

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85.Found: C, 85.24; H, 5.73.

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (3)

White crystals (91%), mp: 234-236 °C. IR (KBr, cm^{-1}): 3365 (b), 3060 (w), 2942 (w), 2821 (w), 1630 (m), 1500 (s), 1446 (m), 1250 (s), 1194 (m), 1032 (m), 969 (m), 790 (s), 765 (s), 700 (s). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.82 (s, 3H), 6.90-6.94 (m, 2H), 7.24-7.28 (m, 6H), 7.51 (s, 4H), 7.78-7.82 (m, 2H), 9.69 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 55.3, 112.1, 114.1, 115.5, 122.8, 126.9, 127.2, 127.9, 128.4, 146.4, 148.9, 151.1, 163.9.

Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.96; H, 5.56. Found: C, 80.83; H, 5.68.

2-(4-Chlorophenyl) -4,5-di-phenyl-1H- imidazole (4)

White crystals (92%), mp: 267-269 °C. IR (KBr, cm^{-1}): 3372 (b), 3048 (w), 2783 (w), 1497 (s), 1114 (m), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.22 (d, 1H, J = 6.6 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.36-7.47 (m, 7H), 7.53 (d, 2H, J = 7.5 Hz), 8.08 (d, 2H, J = 8.4 Hz), 12.77 (s, 1H). ^{13}C NMR (75MHz, DMSO-d_6) δ =127.1, 127.3, 127.5, 128.3, 128.7, 128.9, 129.0, 129.1, 129.2, 129.7, 131.4, 133.2, 135.5, 137.8, 144.9.

Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57. Found: C, 76.13; H, 4.69.

2-(2,4-Dichlorophenyl)-4,5-diphenyl-1H-imidazole (5)

White crystals (91%), mp: 175-177 °C. IR (KBr, cm^{-1}): 3463 (b), 3062 (w), 2941 (w), 2850 (w), 2761 (w), 1654 (m), 1478 (s), 1114 (m), 998 (m), 820 (m), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.22 (d, 1H, J = 6.9 Hz), 7.26-7.31 (m, 2H), 7.35-7.56 (m, 8H), 7.77-7.83 (m, 2H), 12.70 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 127.1, 127.6, 127.9, 128.3, 128.7, 129.2, 129.3, 130.2, 131.2, 132.9, 133.1, 134.3, 135.4, 137.5, 142.8.

Anal. Calcd. for $C_{21}H_{14}Cl_2N_2$: C, 69.05; H, 3.86. Found: C, 68.92; H, 3.97.

2-(2,6-Dichlorophenyl)-4,5-diphenyl-1H-imidazole (6)

White crystals (90%), mp: 235-237 °C. IR (KBr, cm^{-1}): 3392 (m), 3050 (w), 2962 (w), 2846 (w), 1605 (m), 1570 (m), 1443 (s), 1180 (m), 975 (m), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.22 (d, 1H, J = 6.6 Hz), 7.29 (t, 2H, J = 7.8 Hz), 7.35-7.46 (m, 5H), 7.52 (d, 2H, J = 7.2 Hz), 7.56-7.64 (m, 3H), 12.75 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 127.1, 127.7, 127.8, 128.2, 128.3, 128.7, 128.8, 129.3, 130.9, 131.3, 132.4, 135.6, 136.2, 137.0, 141.2.

Anal. Calcd. for $C_{21}H_{14}Cl_2N_2$: C, 69.05; H, 3.86. Found: C, 69.14; H, 3.74.

4-(4,5-Diphenyl-1H-imidazole-2-yl)phenol (7)

Bisque crystals (88%), mp: 267-270 °C. IR (KBr, cm^{-1}):3424 (b), 3317 (m), 3076 (w), 3003 (w), 2638 (b), 1700 (s), 1621 (s), 1500 (s), 1295 (s), 1172 (m), 1035 (m), 850 (m), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.83 (d, 2H, J = 8.1 Hz), 7.19 (d, 1H, J = 6.6 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.34 (d, 1H, J = 6.9 Hz), 7.38-7.52 (m, 6H), 7.87 (d, 2H, J = 8.1 Hz), 9.69 (s,1H), 12.39 (s,1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 115.8, 122.1, 126.8, 127.3, 127.5, 127.8, 128.0, 128.6, 128.8, 129.1, 131.8, 135.9, 137.0, 146.5, 158.2.

Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16. Found: C, 80.87; H, 5.28.

2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (8)

White crystals (84%), mp: 217-220 °C. IR (KBr, cm^{-1}): 3321 (b), 3060 (w), 2941 (w), 2850 (w), 1709 (w), 1610 (m), 1500 (s), 1262 (s), 1033 (s), 765 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 3.79 (s, 3H), 3.83 (s, 3H), 7.04 (d, 1H, J = 8.7 Hz), 7.20 (d, 1H, J = 6.9 Hz), 7.25-7.30 (m, 2H), 7.36 (d, 1H, J = 6.0 Hz), 7.40-7.54 (m, 6H), 7.62-7.65 (m, 2H), 12.51 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 55.9, 56.0, 109.2, 112.2, 118.4, 123.7, 126.9, 127.5, 128.1, 128.6, 128.9, 129.1, 131.7, 135.7, 137.2, 146.2, 149.2, 149.5.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.42; H, 5.78.

4-(4,5-Diphenyl-1H-imidazol-2-yl)-2-methoxyphenol (9)

White crystals (87%), mp: 258-260 °C. IR (KBr, cm^{-1}): 3528 (m), 3061 (w), 2942 (w), 2848 (w), 1613 (m), 1500 (s), 1452 (m), 1296 (s), 1030 (m), 765 (m), 700 (s). ^{1}H NMR

(300 MHz, DMSO-d_6): δ= 3.83 (s, 3H), 6.83 (d, 1H, J = 8.1 Hz), 7.19 (d, 1H, J = 6.6 Hz), 7.27 (t, 2H, J = 7.5 Hz), 7.35 (d, 2H, J = 6.6 Hz), 7.39-7.50 (m, 6H), 7.60 (s, 1H), 9.25 (s, 1H), 12.40 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 56.1, 109.7, 116.0, 118.8, 122.4, 126.8, 127.5, 127.9, 128.1, 128.6, 128.8, 129.1, 131.8, 135.8, 146.5, 147.3, 147.5, 148.1.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30. Found: C, 77.26; H, 5.19.

(E)-4,5-Diphenyl-2-styryl-1H-imidazole (10)

Bisque crystals (90%), mp: 254-256 °C. IR (KBr, cm^{-1}): 3412 (b), 3078 (w), 2863 (w), 1623 (m), 1482 (m), 995 (m), 764 (s), 700 (s). ^{1}H NMR (250 MHz, DMSO-d_6): δ= 7.25-7.26 (m, 2H), 7.33 (d, 4H, J = 6.5 Hz), 7.37-7.45 (m, 5H), 7.48-7.56 (m, 4H), 7.91 (d, 2H, J = 7.7 Hz), 9.42 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 125.7, 127.0, 127.5, 128.3, 128.7, 128.9, 129.2, 130.8, 131.6, 135.6, 137.6, 146.0.

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63. Found: C, 85.57; H, 5.74.

4-(4,5-Diphenyl-1H-imidazol-2-yl)-N,N-dimethylbenzenamine (11)

Bisque crystals (87%), mp: 262-264 °C. IR (KBr, cm^{-1}): 3474 (b), 3071 (w), 2887 (w), 2818 (w), 1625 (s), 1500 (s), 1372 (m), 1200 (m), 834 (m), 765 (m), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 2.90 (s, 6H), 6.77 (d, 2H, J = 8.4 Hz), 7.18 (d, 1H, J = 6.9 Hz), 7.27 (t, 2H, J = 7.5 Hz), 7.32 (d, 1H, J = 6.6 Hz), 7.37-7.40 (m, 3H), 7.45 (t, 2H, J = 7.5 Hz), 7.50-7.52 (m, 1H), 7.88 (d, 2H, J = 8.7 Hz), 12.3 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 112.4, 118.8, 126.7, 127.5, 127.9, 128.6, 128.7, 129.1, 131.9, 135.9, 136.9, 146.9, 150.7.

Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24. Found: C, 81.49; H, 6.15.

2-(Anthracen-10-yl)-4,5-diphenyl-1H-imidazole (12)

Bisque crystals (76%), mp: 165-167 °C. IR (KBr, cm^{-1}): 3401 (m), 3063 (m), 2941 (w), 1618 (m), 1500 (s), 1342 (m), 775 (m), 742 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.24-7.41 (m, 6H), 7.55-7.63 (m, 8H), 7.90-7.91 (m, 2H), 8.15-8.17 (m, 2H), 8.78 (s, 1H), 12.94 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ= 126.1, 126.5, 127.1, 127.8, 128.0, 128.2, 128.4, 128.8, 128.9, 129.2, 131.3, 131.6, 135.9, 137.4, 143.7.

Anal. Calcd. for $C_{29}H_{20}N_2$: C, 87.41; H, 5.56. Found: C, 87.52; H, 5.67.

4-(4,5-Diphenyl-1H-imidazol-2-yl)benzonitrile (13)

Bisque crystals (89%), mp: 232-233 °C. IR (KBr, cm^{-1}): 3410 (b), 3054 (m), 2227 (s), 1610 (s), 1490 (s), 850 (m), 766 (s), 700 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.22-7.30 (m, 3H), 7.42-7.54 (m, 7H), 7.93 (d, 2H, J = 7.8 Hz), 8.23 (d, 2H, J = 8.1 Hz), 13.01 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 110.6, 119.4, 126.0, 127.3, 127.6, 128.6, 128.7, 129.0, 129.2, 130.1, 131.1, 133.3, 134.7, 135.1, 138.5, 144.2.

Anal. Calcd. for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70. Found: C, 82.09; H, 4.57.

2-(Furan-2-yl)-4,5-diphenyl -1H-imidazole(14)

Bisque crystals (91%), mp: 234-235 °C. IR (KBr, cm^{-1}): 3413 (b), 3079 (w), 2818 (w), 2736 (w), 1453 (m), 1012 (m), 771 (s), 700 (s). ^{1}H NMR (250 MHz, DMSO-d_6): δ= 6.50-6.53 (m, 1H), 9.98 (d, 1H, J=3.2 Hz), 7.26-7.33 (m, 7H), 7.45-7.52 (m, 4H), 9.68 (s, 1H).^{13}C NMR (75 MHz, DMSO-d_6): δ= 107.9, 112.3, 127.7,128.2, 128.9, 139.0, 143.6, 146.1.

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93. Found: C, 79.57; H, 5.08.

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