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A facile synthesis of 6-(1,3,4-oxadiazol-2-yl)-N-arylylpyridin-3-amines

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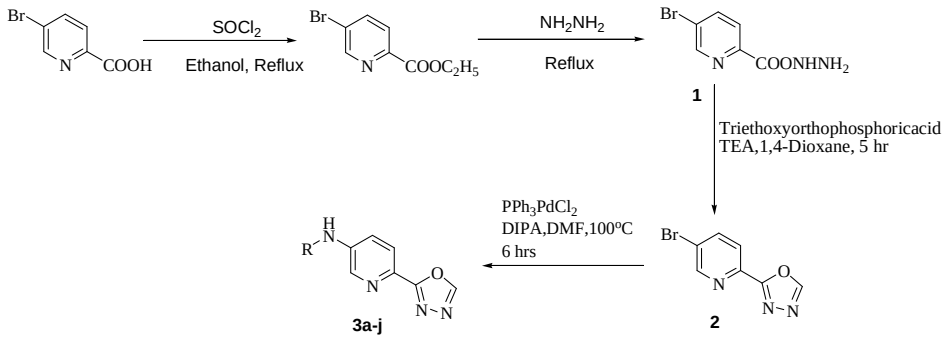
ABSTRACT

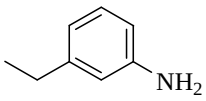
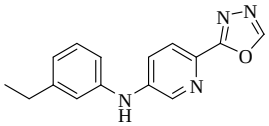
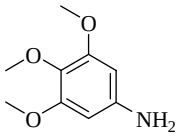
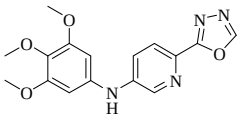
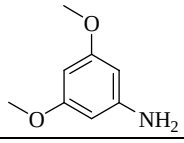
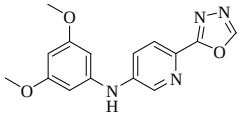
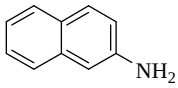
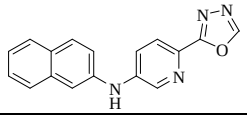
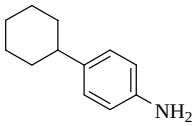
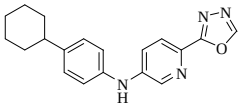
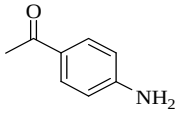
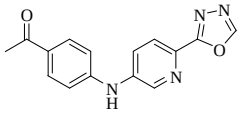
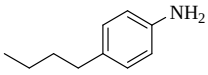
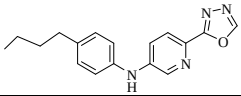
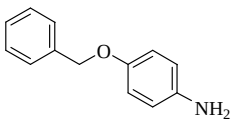
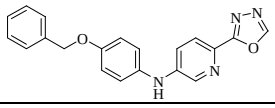
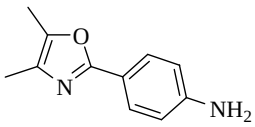
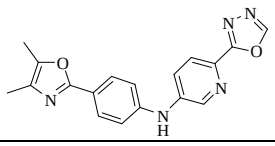
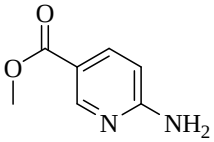
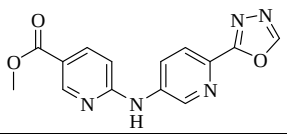
*5-bromopyridine-2-carbohydrazide **(1)** cyclised with Triethoxyorthophosphoricacid to form 5-bromo-2-(1,3,4-oxadiazol-2-yl)pyridine **(2)**, which on reaction with triphenylpalladiumchloride offer 6-(1,3,4-oxadiazol-2-yl)-N-arylylpyridin-3-amine **(3a-j)**.*

INTRODUCTION

The considerable biological and medicinal activities of poly functionally substituted pyridines[1-3] and condensed pyridine[4-8] have stimulated considerable recent research aimed at developing syntheses of these compounds. Pyridine derivatives exhibited various types of biological activities viz antimicrobial[9], antibacterial[10-13], antimycobacterial[14, 15], analgesic antiparkinsonian[16-18], anticonvulsant[18], antitumoral[19, 20], cytotoxic[21-25], antimalarial[26], antidiabetic[27], pesticidal[28], inhibitory[29-32] and receptor antagonists[33]. Considerable evidence has accumulated during the past two decades demonstrating the various pharmacological effects of 1,3,4-oxadiazoles, which include antibacterial[34], antifungal[35], anthelmintic[36], antitubercular[37], anticancer[38], anti-HIV[39], antioxidant[40], analgesic[41], anti-inflammatory[42] and anticonvulsant[43] activities. In spite of the large number of antibiotics and chemotherapeutics currently available for medical usage, the spectra of increasing bacterial resistance has made it necessary to continue the search for new antimicrobial substances. To this end a large number of oxadiazole derivatives have been prepared.

Scheme



Compound	Amine(R)	Product	Molecular formula	Time(hr)	Yield(%)
3a			C15H14N4O	7	70
3b			C16H16N4O4	7	68
3c			C15H14N4O3	8	69
3d			C17H12N4O	8	71
3e			C19H20N4O	9	68
3f			C15H12N4O2	7	73
3g			C17H18N4O	8	68
3h			C20H16N4O2	7	72
3i			C18H15N5O2	9	66
3j			C14H11N5O3	10	64

MATERIALS AND METHODS

Experimental Section

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The ^{1}H NMR was recorded in the indicated solvent on a Varian 400 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 F_{254}).

5-Bromo-2-(1,3,4-oxadiazol-2-yl)pyridine (2)

5-bromopyridine-2-carbohydrazide (0.01 mole) dissolved in 1,4-dioxane and TEA (0.01 mole) added at RT. The contents were stirred for 15min, reaction mass cooled to 0^{o}C, at and Triethoxy orthoformate (0.01 mole) was added and stirred at reflux for 5hrs.The reaction was monitored by TLC, after the completion of reaction, it is poured on to ice water, extracted with ethylacetate twice, organic layer dried over Na_2SO_4.

^{1}H NMR (400 MHz, DMSO-d_6): δ=9.46 (s, 1H),8.95 (d, 1H,J=2 Hz), 8.34 (dd,1H, J= 8.2 Hz,2.8 Hz),8.15 (d,1H, J= 8.4 Hz); Mass m/z = 227 (M^++1)

6-(1,3,4-Oxadiazol-2-yl)-N-arylylpyridin-3-amine (3a-j)

5-bromo-2-(1,3,4-oxadiazol-2-yl)pyridine (2) (0.01 mole) dissolved in 1,4-dioxane and K_2CO_3 and $Pd_2(dba)_3$ were added, then degased for 10min. Xanthphos added again degased for 10min. To the above contents different amines (0.01 mole) is added under N_2 condition, reaction mass stirred at 80^{o}C for 6hrs. Reaction mass filtered through celite bed, filtrate taken and concentrated, recrystalised from EtOH.

N-(3-Ethylphenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3a)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.28 (s, 1H), 8.93 (brs, 1H), 8.43 (d, 1H, J= 8.8 Hz), 7.99 (d, 1H, J= 8.0Hz), 7.57 (dd, 1H, J=8.8 Hz, 2.8 Hz), 7.37 (d, 1H, J= 4.8 Hz), 7.26 (t, 1H, J=7.6 Hz), 7.05 (s, 1H), 6.89 (d, 1H, J=7.2 Hz), 2.6 (q, 2H), 1.21 (t, 3H); Mass m/z = 267 (M^++1)

N-(3,4,5-Trimethoxyphenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3b)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.32 (s, 1H), 8.96 (brs, 1H), 8.52 (d, 1H, J= 2.8 Hz), 8.02 (d, 1H, J= 7.8 Hz), 7.62 (dd, 1H, J=7.8 Hz), 7.62 (d, 1H, J= 7.8 Hz), 7.62 (dd, 1H, J=8.4 Hz), 7.52 (s, 2H), 3.76 (s, 3H), 3.70 (s, 3H); Mass m/z = 329 (M^++1)

N-(3,5-Dimethoxyphenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3c)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.33 (s, 1H), 8.96 (brs, 1H), 8.53 (d, 1H, J= 2.8 Hz), 8.01 (d, 1H, J= 7.8 Hz), 7.63 (dd, 1H, J=8.2 Hz, J= 2.8 Hz), 7.53 (s, 2H), 7.45 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H); Mass m/z = 299 (M^++1)

N-(Naphthalen-2-yl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3d)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.28 (s, 1H), 8.93 (brs, 1H), 8.54 (d, 1H, J= 2.4 Hz), 8.05 (d, 1H, J= 8.0 Hz), 7.64 (dd, 1H, J=8.2 Hz, J= 2.8 Hz), 7.51 (d, 1H, J= 7.6 Hz), 7.48 (s, 1H), 7.46 (d, 1H, J= 7.6 Hz), 7.44-7.40 (m, 4H); Mass m/z = 289 (M^++1)

N-(4-Cyclohexylphenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3e)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.29 (s, 1H), 8.90 (brs, 1H), 8.50 (d, 1H, J= 2.2 Hz), 8.00 (d, 1H, J= 7.8 Hz), 7.65 (dd, 1H, J=8.0 Hz, J= 2.4 Hz), 7.52 (d, 2H), 7.48 (d, 2H), 3.12 (m, 1H), 1.35-1.12 (m, 10H); Mass m/z = 321 (M^++1)

1-(4-(6-(1,3,4-Oxadiazol-2-yl)pyridin-3-ylamino)phenyl)ethanone (3f)

^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.25 (s, 1H), 8.80 (brs, 1H), 8.50 (d, 1H, J= 2.2 Hz), 7.99 (d, 1H, J= 7.8 Hz), 7.60 (dd, 1H, J=8.2 Hz, J= 2.2 Hz), 7.48 (d, 2H), 7.35 (d, 2H), 2.10 (s, 3H), 1.92 (m, 4H), 1.10 (t, 3H); Mass m/z = 281 (M^++1)

N-(4-Butylphenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3g)
^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.24 (s, 1H), 8.91 (brs, 1H), 8.61 (d, 1H, J= 2.4 Hz), 7.99 (d, 1H, J= 7.8 Hz), 7.65 (dd, 1H, J=8.0 Hz, J= 2.4 Hz), 7.52 (d, 2H), 7.45 (d, 2H), 2.61 (t, 2H); Mass m/z = 295 (M^++1)

N-(4-(Benzyloxy)phenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3h)
^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.20 (s, 1H), 8.95 (brs, 1H), 8.65 (d, 1H, J= 2.8 Hz), 7.99 (d, 1H, J= 7.8 Hz), 7.66 (dd, 1H, J=8.0 Hz, J= 2.8 Hz), 7.60 (d, 2H), 7.45 (d, 2H), 7.42-7.28 (m, 5H), 5.21 (s, 2H); Mass m/z = 245 (M^++1)

N-(4-(4,5-Dimethyloxazol-2-yl)phenyl)-6-(1,3,4-oxadiazol-2-yl)pyridin-3-amine (3i)
^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.30 (s, 1H), 8.99 (brs, 1H), 8.52 (d, 1H, J= 2.8 Hz), 8.02 (d, 1H, J= 7.8 Hz), 7.61 (dd, 1H, J=8.8 Hz, J= 2.8 Hz), 7.55 (d, 2H), 7.44 (d, 2H), 2.95 (s, 3H), 2.70 (s, 3H); Mass m/z = 334 (M^++1)

Methyl 6-(6-(1,3,4-oxadiazol-2-yl)pyridin-3-ylamino)pyridine-3-carboxylate (3j)
^{1}H NMR(400 MHz, DMSO-d_6): δ= 9.20 (s, 1H), 9.11 (s, 1H), 8.90 (brs, 1H), 8.60 (d, 1H, J= 3.2 Hz), 8.55 (d, 1H, J= 3.0 Hz), 8.05 (d, 1H, J=7.8 Hz), 7.98 (d, 1H, J=8.0Hz), 7.65 (dd, 1H, J=8.2 Hz), 7.60 (dd, 1H, J=8.8 Hz), 3.86 (s, 3H); Mass m/z = 298 (M^++1)

CONCLUSION

We have developed an efficient protocol for the synthesis and characterization of A facie synthesis of 6-(1,3,4-oxadiazol-2-yl)-N-arylylpyridin-3-amines. Operational simplicity, cleaner reaction, easer workup and are environmentally-friendly reactions.

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