Synthesis of 4-substituted oxazolo[4,5-c]quinolines by direct reaction at C-4 position of oxazole

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Procedures for preparation of compounds 2, 3 and 6

Synthesis of 5-(2-nitrophenyl)oxazole (2): To a mixture of 2-nitrobenzaldehyde (5g, 0.033 mol) and tosylmethylisocyanide (7.748g, 0.039 mol) in 30 ml of MeOH was added K$_2$CO$_3$ (9.15g, 0.066 mol). The solution was refluxed for 6 hrs and then solvent was removed under reduced pressure. The residue was poured in to water and extracted with ethyl acetate. The organic layer was washed with brain and dried over Na$_2$SO$_4$. Organic layer was concentrated in vacuo and residue was purified by column chromatography with 15% ethylacetate/ hexane as a eluent.

Yield: 83%(5.14 g). Light brown solid, mp 71 °C. R$_f$ = 0.5(Hexane / Ethyl acetate = 8:2 ). IR (KBr, cm$^{-1}$): 3112, 1520, 1348,1105.$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.36 (s, 1H), 7.51 (dd, $J$ = 12.3, 4.5 Hz, 1H), 7.65 (dt, $J$ = 15.2, 6.4 Hz, 2H), 7.81 (d, $J$ = 8.1 Hz, 1H), 7.95 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 121.49, 124.43, 125.77, 129.66, 129.83, 132.65, 146.47, 147.38, 151.68. ESI-MS: 191(M+H$^+$)

Synthesis of 2-(oxazol-5-yl)aniline (3): To a solution of o-nitrophenyloxazole (2g, 0.0105 mol) in 25 ml of methanol Fe (5.8g, 0.105mol) and 1ml of HCl were added and the reaction mixture was stirred at 60 °C for 8h. The reaction mixture was cooled to RT and passed through celite pad the solvent was evaporated. The residue was diluted with water and neutralized with NaHCO$_3$, extracted with ethyl acetate. The organic layer was washed with brain and dried over Na$_2$SO$_4$. Organic layer was concentrated in vacuo and residue was purified by column chromatography with 20% ethylacetate/ hexane as a eluent.

Yield: 68%(1.14 g) brown colour liquid, R$_f$ = 0.5(Hexane / Ethyl acetate = 7:3). IR (KBr, cm$^{-1}$): 3410, 3127, 2889, 1598, 1504, 1312, 1103. $^1$H NMR (300 MHz, DMSO) δ 5.34 (s, 2H), 6.66 (t, $J$ = 7.5 Hz, 1H), 6.84 (d, $J$ = 8.1 Hz, 1H), 7.09 (t, $J$ = 7.6 Hz, 1H), 7.42 (d, $J$ = 7.7 Hz, 1H), 8.40 (s, 1H), 7.49 (s, 1H). $^{13}$C NMR (75 MHz, DMSO): δ 111.99, 116.91, 117.08, 122.64, 127.27, 129.87, 145.38, 149.74, 151.11. ESI-MS: 161(M+H$^+$)
Synthesis of 3-(oxazol-5-yl)pyridin-2-amine (6): To a mixture of 2-amino-3-pyridinecarboxaldehyde (0.8g, 0.00655mol) and tosylmethylisocyanide (1.5g, 0.00786 mol) in 30 ml of MeOH was added K$_2$CO$_3$ (1.8g, 0.013 mol). The solution was refluxed for 6 hrs and then solvent was removed under reduced pressure. The residue was poured in to water and extracted with ethyl acetate. The organic layer was washed with brain and dried over Na$_2$SO$_4$ organic layer was concentrated in vacuo and residue was purified by column chromatography with 40% ethylacetate/ hexane as an eluent.

Yield: 71.02%(0.745 g) Brown solid, mp 86 °C. R$_f$ = 0.5(Hexane / Ethyl acetate = 6: 4). IR (KBr, cm$^{-1}$): 3446, 3304, 3142,1643, 1569, 464, 1131. $^1$H NMR (300 MHz, DMSO) δ 8.45 (s, 1H), 8.02 (d, $J$ = 4.4 Hz, 1H), 7.75 (d, $J$ = 7.4 Hz, 1H), 7.59 (s, 1H), 6.69 (dd, $J$ = 7.5, 4.9 Hz, 1H), 6.11 (s, 2H). $^{13}$C NMR (75 MHz, DMSO): δ 107.08, 113.25, 123.44, 135.29, 148.10, 148.90, 151.84, 155.46. HRMS-ESI (m/z): Calcd for C$_8$H$_8$N$_3$O [M+H]$^+$, 162.0667 found 162.0668.
$^1$H NMR (300 MHz, CDCl$_3$) 5-(2-nitrophenyl)oxazole (2)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 5-(2-nitrophenyl)oxazole
$^1$H-NMR(300 MHz, DMSO-d$_6$) 2-(oxazol-5-yl)aniline (3)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 2-(oxazol-5-yl)aniline
\(^1\)H-NMR(300 MHz, DMSO-d\(_6\)) 3-(oxazol-5-yl)pyridin-2-amine (6)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 3-(oxazol-5-yl)pyridin-2-amine
$^1$H-NMR(300 MHz, DMSO-d$_6$) 4-phenyloxazolo[4,5-c]quinoline (4a)
$^{13}$C-NMR (75.5 MHz, DMSO-$d_6$) 4-phenyloxazolo[4,5-c]quinoline (4a)
$^{13}\text{C-NMR}(75.5 \text{ MHz, DMSO-}d_6)$ 4-(4-nitrophenyl)oxazolo[4,5-c]quinoline (4b)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 4-(4-nitrophenyl)oxazolo[4,5-c]quinoline (4b)
$^1$H-NMR(300 MHz, DMSO-d$_6$) 4-(4-(trifluoromethyl)phenyl)oxazolo[4,5-c]quinoline (4c)
$^{13}$C-NMR(75.5 MHz, DMSO-d$_6$) 4-(4-(trifluoromethyl)phenyl)oxazolo[4,5-c]quinoline (4c)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(thiophen-2-yl)oxazolo[4,5-c]quinoline (4d)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(thiophen-2-yl)oxazolo[4,5-c]quinoline (4d)

![Chemical Structure of 4-(thiophen-2-yl)oxazolo[4,5-c]quinoline](image)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(4-methoxyphenyl)oxazolo[4,5-c]quinoline (4e)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(4-methoxyphenyl)oxazolo[4,5-c]quinoline (4e)
$^1$H-NMR (300 MHz, DMSO-d$_6$) 2-(oxazolo[4,5-c]quinolin-4-yl)phenol (4f)
$^{13}$C-NMR (75.5 MHz, DMSO-$d_6$) 2-(oxazolo[4,5-c]quinolin-4-yl)phenol (4f)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(3,4-dimethoxyphenyl)oxazolo[4,5-c]quinoline (4g)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(3,4-dimethoxyphenyl)oxazolo[4,5-$c$]quinoline (4g)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(4-chlorophenyl)oxazolo[4,5-c]quinoline (4h)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(4-chlorophenyl)oxazolo[4,5-c]quinoline (4h)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(4-fluorophenyl)oxazolo[4,5-c]quinoline (4i)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(4-fluorophenyl)oxazolo[4,5-c]quinoline (4i)
$^1$H NMR (300 MHz, CDCl$_3$) 4-(4-bromophenyl)oxazolo[4,5-c]quinoline (4j)
$^{13}$C NMR (75.5 MHz, CDCl$_3$) 4-(4-bromophenyl)oxazolo[4,5-c]quinoline (4j)
$^1$H-NMR (300 MHz, DMSO-d$_6$) 4-(3-nitrophenyl)oxazolo[4,5-c]quinoline (4k)
$^{13}$C-NMR(75.5 MHz, DMSO-d$_6$) 4-(3-nitrophenyl)oxazolo[4,5-c]quinoline (4k)
$^1$H-NMR (300 MHz, DMSO-d$_6$) 4-(3-(trifluoromethyl)phenyl)oxazo[4,5-c]quinoline (4l)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 4-(3-(trifluoromethyl)phenyl)oxazolo[4,5-c]quinoline (4l)
'H-NMR (300 MHz, DMSO-d$_6$) 4-phenyloxazolo[4,5-c][1,8]naphthyridine (7a)
$^{13}$C-NMR(75.5 MHz, DMSO-d$_6$) 4-phenyloxazo[4,5-c][1,8]naphthyridine (7a)
$^1$H-NMR(300 MHz, DMSO-d$_6$) 4-(4-methoxyphenyl)oxazolo[4,5-c][1,8]naphthyridine (7b)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 4-(4-methoxyphenyl)oxazolo[4,5-c][1,8]naphthyridine (7b)
$^1$H-NMR (300 MHz, DMSO-d$_6$) 2-(oxazolo[4,5-c][1,8]naphthyridin-4-yl)phenol (7c)
$^{13}$C-NMR (75.5 MHz, DMSO-d$_6$) 2-(oxazolo[4,5-c][1,8]naphthyridin-4-yl)phenol (7c)
$^1$H-NMR (300 MHz, DMSO-d$_6$) 4-(thiophen-2-yl)oxazolo[4,5-c][1,8]naphthyridine (7d)
\(^{13}\)C-NMR (75.5 MHz, DMSO-\(d_6\)) 4-(thiophen-2-yl)oxazolo[4,5-\(c\)] [1,8]naphthyridine (7d)