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A Facile Protocol for the Construction of Tricyclic Framework Tetrahydrobenzo-4-nitrobenzenesulfonate, 4-methylbenzenesulfonate and [1,8] naphthyridine Substituents from Methyl δ-Lactam

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A convenient procedure for the preparation of various naphthyridine constructions is described. The method is based on the Vilsmeier, cyclization and Suzuki reactions of piperidinone with substituted aniline. The reactions provided the desired fused tricyclic heterocycles products in high yields.

Key words: lactam, Vilsmeier intermediate, cyclization processes, Suzuki reactions.

INTRODUCTION

The search for potent chemotherapeutic agents with anticancer activity and issued from natural sources is still attracting a wide interest as drug-resistance tends to proliferate.The synthesis of alkaloids, which has been described in excellent reviews has little been explored if one except the largely investigated area of the catharanthus roseus alkaloids[1,2]. More recent work on indole alkaloids has focused on the complex haplophytine which has finally succumbed recently to total synthesis. However, recent work by Kam, Morita and co-workers[3-8]have been isolated unique bis-indole alkaloids which called *Leucophyllidine* and found active against the cancer disease[9]. New biologically relevant indole alkaloids continue to be discovered that might be considering for future clinical applications[10]. Due to the limited supply from natural sources, synthesis will also constitute a viable alternative to extraction. The development of new synthetic methods[11], using, or not, biomimetic pathways, should thus allow an easier access to larger quantities of these bioactive targets and open the way for further biological studies.

EXPERIMENTAL

General: Equipment, Chemicals and Work Technique

All reactions were carried out under argon atmosphere with dry solvents under anhydrous conditions. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Commercial reagents were used without purification. Benzene was distilled over sodium and benzophenone.DCE were distilled from CaH_2.^{1}H NMR and ^{13}C NMR were recorded on Bruker DPX-200 FT (^{1}H: 200 MHz, ^{13}C: 50.3 MHz), Bruker Advance-300FT (^{1}H: 300 MHz, ^{13}C: 75.5 MHz),. All NMR spectra present in this work were measured in $CDCl_3$ solution. All chemical shifts are given in ppm.The chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hz respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High resolution mass spectra were recorded on a Micromass ZABSpec TOF, on a Q-Tof Applied Biosystems and on Waters Q-Tof 2 apparatus. IR spectra were recordedon a Perkin-Elmer 1710 spectrophotometer or on a Perkin-Elmer aragon 1000 FT-IR spectrophotometer

Thin Layer Chromatography (TLC)

Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. Column chromatography was performed with Merck Silica Gel 60 (70-230 mesh), (230-400 mesh ASTM) and Baker silica gel (0.063-0.200 mm) were used for flash chromatography.

General Procedure for Preparation of Amidines (A)[12]

A mixture of methyl piperidinone (6 g, 53.02 mmol, 1 eq.) in dry DCM 60 mL and $SOCl_2$ (7.6 mL, 109 mmol, 2.05 eq.) was stirred for 1.5h at room temperature. To the reaction a solution of ester aniline substituents (53.55 mmol, 1.05 eq.) in DCM (20 mL) was added dropwise and was heated to 40°C overnight. Ice-cold water was then added followed by a 30% NaOH solution to alkaline pH. The organic solvents were concentrated under vacuum, the extracted with DCM, brine and dried over $MgSO_4$. The solvent then washed with evaporated in vacuum and the crude purified by chromatography on silica gel(petroleum ether/ethyl acetate) to provide the desired products (**5-7**) as a pale yellow solid.

(E)-methyl 2-((1-methylpiperidin-2-ylidene) amino) benzoate(5)

Yield 11.75 g (90%) as a pale yellow solid.**M.p** = 80-81°C.**R$_f$** = 0.4 (petroleum ether/ethyl acetate 80:20). IR (ATR) ν_{max}(cm^{-1}) =2930, 1720, 1629, 1591, 1239, 1072, 1015, 720. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.95 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.50-7.46 (m, 1H, CH_{ar}), 7.42-7.35 (m, 2H, CH_{ar}), 3.94 (s, 3H, CH_3), 3.39 (t, 1H, *J* = 3.3 Hz, C<u>H</u>), 3.35 (appearant t, 1H, *J* = 3 and 3.3 Hz, CH), 2.82 (s, 3H, CH_3), 2.45 (t, 2H, *J* = 3.6 Hz, CH_2), 1.66-1.59 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$, 75.5 MHz): ä (ppm) = 166.5 (C=O), 160.8 (C=N), 146.6 (C_{ar}), 132.9 (C_{ar}), 131.2 (C_{ar}), 121.3 (C_{ar}), 120.4 (C_{ar}), 113.6 (C_{ar}), 52.1 (C_{ar}), 49.5 (C), 36.3 (C), 30.2 (C), 24.7 (C), 22.5 (C).HRMS (ESI): $[M+H]^+$ $C_{14}H_{19}N_2O_2$: calcd. 247.1446, found 247.1445.

(E)-methyl 4-methyl-2-((1-methylpiperidin-2-ylidene)amino)benzoate(6)

Yield 12.97g(94%) as a pale yellow solid.M.p = 94-95°C.R_f= 0.39 (petroleum ether/ethyl acetate 80:20). IR (ATR) ν_{max}(cm^{-1}) = 2930, 1720, 1627, 1590, 1239, 1071, 1015, 721. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.88 (dd, 1H, *J* = 4.5 Hz, CH_{ar}), 7.35 (d, 1H, *J* = 0.9 Hz, CH_{ar}), 7.23 (dd, 1H, *J* = 0.9 and 1.5 Hz, CH_{ar}), 3.90 (s, 3H, CH_3), 3.40-3.36 (m, 2H, C<u>H</u>$_2$), 2.83 (s, 3H, CH_3), 2.50 (t, 2H, *J* = 3.6 Hz, CH_2), 2.36 (s, 3H, CH_3), 1.68-1.58 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 166.5 (C=O), 160.8 (C=N), 146.5 (C_{ar}), 145.0 (C_{ar}), 128.8 (C_{ar}), 122.1 (C_{ar}), 120.1 (C_{ar}), 111.5 (C_{ar}), 52.1 (C), 49.5 (C), 36.3 (C), 30.3 (C), 24.7 (C), 22.5 (C), 21.2 (C).HRMS (ESI): $[M+H]^+$ $C_{15}H_{21}N_2O_2$: calcd. 261.1603, found 261.1604.

(E)-methyl 4,5- dimethyl -2-((1-methylpiperidin-2-ylidene) amino) benzoate (7)

Yield 13.96 g (96%) as a pale yellow solid.M.p = 119-120°C.R_f= 0.39 (petroleum ether/ ethyl acetate 80:20). IR (ATR) ν_{max}(cm^{-1}) = 2930, 1720, 1627, 1590, 1239, 1071, 1015, 721. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.82 (s, 1H, CH_{ar}), 7.30 (s, 1H, C<u>H</u>$_{ar}$), 3.94 (s, 3H, CH_3), 3.39 (t, 1H, *J* = 3.3 Hz, CH), 3.35 (t, 1H, *J* = 3.3 Hz, CH), 2.82 (s, 3H,

CH_3), 2.45 (t, 2H, *J* = 3.6 Hz, C$\underline{H}_2$), 2.36 (s, 6H, 2CH_3), 1.66-1.59 (m, 4H, 2CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 166.2 (C=O), 160.8 (C=N), 144.8 (C_{ar}), 143.2 (C_{ar}), 131.9 (C_{ar}), 127.8 (C_{ar}), 122.1 (C_{ar}), 121.5 (C_{ar}), 52.1 (C), 49.3 (C), 36.3 (C), 30.2 (C), 24.7 (C), 22.5 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{16}H_{23}N_2O_2$: calcd. 275.1759, found 275.1758.

General Procedure for Preparation of Phenols (B)

A mixture of potassium *tert*-butoxide (66 mg, 5.85 mmol, 2.5 eq.) in dry THF (15 mL) and solution of amidines substituents (2.34 mmol, 1 eq.) was stirred at room temperature for 6h.The reaction mixture was quenched with NH_4Cl, concentrated under reduced pressure and extracted with DCM, brine and dried over $MgSO_4$. The solvent evaporated *in vacuo* and purified by chromatography on silica gel(petroleum ether/ethyl acetate) to provide the desired products (**8-10**) as a white solid.

1-methyl-1,2,3,4-tetrahydrobenzo [b][1,8] naphthyridin-5-ol (8)

Yield 0.456 mg (91%) as a white solid.M.p = 124-125°C.R_f= 0.33 (petroleum ether/ethyl acetate 70:30). IR (ATR) ν_{max}(cm^{-1}) = 2920, 1554, 1490, 1470, 1389, 769. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.71 (dd, 1H, *J* = 0.9 and 4.5 Hz, C$\underline{H}_{ar}$), 7.60 (dd, 1H , *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.21 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.10 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.45 (t, 2H, *J* = 3 Hz, CH_2), 2.89 (s, 3H, CH_3), 2.83 (appearant t, 2H, *J* = 3.3 and 3.6 Hz, CH_2), 2.00-1.95 (m, 2H, CH_2), 1.29 (s, 1H, O$\underline{H}$). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 164.7 (C=N), 150.9 (C_{ar}), 142.7 (C_{ar}), 131.1 (C_{ar}), 127.0 (C_{ar}), 124.8 (C_{ar}), 123.9 (C_{ar}), 115.9 (C_{ar}), 111.4 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 19.6 (C).HRMS (ESI): $[M+H]^+$ $C_{13}H_{15}N_2O$: calcd. 215.1184, found 215.1186.

1,8-dimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-ol (9)

Yield 0.560 mg (92%) as a white solid.M.p = 142-144°C.R_f= 0.32 (petroleum ether/ethyl acetate 70:30). IR (ATR) ν_{max}(cm^{-1}) = 2920, 1625, 1497, 1471, 1391, 760. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.71 (dd, 1H, *J* = 0.9 and 4.5 Hz, C$\underline{H}_{ar}$), 7.59 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.21 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.10 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.44 (appearant t, 2H, *J* = 3 and 3.3 Hz, C$\underline{H}_2$), 2.89 (s, 3H, C$\underline{H}_3$), 2.83, (appearant t, 2H, *J* = 3.3 and 3.6 Hz, CH_2), 2.24 (t, 3H,CH3), 2.00-1.95 (m, 2H, CH_2), 1.29 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 164.7 (C=N), 150.9 (C_{ar}), 142.7 (C_{ar}), 141.2 (C_{ar}), 131.1 (C_{ar}), 127.0 (C_{ar}), 124.8 (C_{ar}), 123.9 (C_{ar}), 115.9 (C_{ar}), 111.4 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 19.6 (C).HRMS (ESI): $[M+H]^+$ $C_{14}H_{17}N_2O$: calcd. 229.1941, found 229.1940.

1,7,8-trimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-ol (10)

Yield 0.603 mg (94%) as a white solid. M.p = 163-164° C.R_f= 0.31 (petroleum ether/ethyl acetate 70:30). IR (ATR) ν_{max}(cm^{-1}) = 2920, 1553, 1497, 1470, 1391, 1008, 760. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.34 (s, 1H, CH_{ar}), 7.18 (s, 1H, CH_{ar}), 3.44 (t, 2H, *J* = 3.3 Hz, CH_2), 2.89 (s, 3H, CH_3), 2.82 (t, 2H, *J* = 3.6 Hz, CH_2), 3.43 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.00-1.95 (m, 2H, CH_2), 1.25 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 164.3 (C=N), 152.1 (C_{ar}), 141.1 (C_{ar}), 139.2 (C_{ar}), 135.7 (C_{ar}), 127.1 (C_{ar}), 120.4 (C_{ar}), 117.5 (C_{ar}),112.2 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 20.0 (C), 19.6 (C).HRMS (ESI): $[M+H]^+$ $C_{15}H_{19}N_2O$: calcd. 243.1497, found 243.1498.

General Procedure for Preparation of Nitrobenzene Sulfonates (C)[13]

To a mixture of phenol substituents (0.185 mmol, 1 eq.) in freshly distillated DCM (2 mL) and triethyl amine (19 µL, 0.185 mmol, 1 eq.) p-nitrobenzene sulfonyl chloride (41 mg, 0.185, 1 eq.) in DCM was added dropwise and stirred for 10h at room temperature. The solvent evaporated *in vacuo*, the crude material then dissolved in EtOAc and washed with 1N HCl, 1N NaOH and saturated NaCl solution. The organic phase was dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (DCM/ MeOH) to provide the desired products (**11-13**) as an orange solid.

1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl 4-nitrobenzenesulfonate1 (11)

Yield 61 mg (83%) as an orange solid.M.p = 199-201°C.R_f= 0.4 (DCM/MeOH98:2). IR (ATR) ν_{max}(cm^{-1}) = 2960, 1255, 1081, 1018, 790, 780. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.42 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 8.08 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.86 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.74 (dd, 1H, *J* =

0.9 and 4.5 Hz, CH_{ar}), 7.25 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.17 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_3), 3.48 (t, 1H, *J* = 3.3 Hz, CH), 3.38 (t, 1H, *J* = 3.3 Hz, CH), 2.90 (s, 3H, CH_3), 2.63 (t, 2H, *J* = 3.3 Hz, CH_2), 2.04-1.99 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.7 (C_{ar}), 152.9 (C_{ar}), 147.3 (C_{ar}), 145.9 (C_{ar}), 144.8 (C_{ar}), 131.9 (C_{ar}), 130.3 (C), 127.7 (C_{ar}), 127.3 (C_{ar}), 124.7 (C_{ar}), 124.3 ($2C_{ar}$), 124.0 ($2C_{ar}$), 123.4 (C), 48.6 (C), 37.8 (C), 22.9 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{19}H_{18}N_3O_5S$: calcd. 400.0967, found 400.0965.

1,8-dimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-4-nitrobenzenesulfonate (12)

Yield, 69 mg (86%) as an orange solid.M.p = 229-230°C.R_f= 0.4 (DCM/MeOH98:2). IR (ATR) ν_{max}(cm^{-1}) = 2960, 1255, 1018, 790, 780.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.48 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 8.22 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.73 (d, 1H, *J* = 4.5 Hz, CH_{ar}), 7.58 (d, 1H, *J* = 0.6 Hz, CH_{ar}), 7.13 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.45 (appearant t, 1H, *J* = 3.3 and 3 Hz, CH), 3.41 (t, 1H, *J* = 3.3 Hz, CH), 2.97 (t, 2H, *J* = 3.6 Hz, CH_2), 2.91 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.01-1.96 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.2 (C_{ar}), 153.8 (C_{ar}), 147.3 (C_{ar}), 145.9 (C_{ar}), 143.6 (C_{ar}), 141.2 (C_{ar}), 130.3 (2C), 128.0 (C_{ar}), 126.8 (C_{ar}), 125.3 (C_{ar}), 124.3 ($2C_{ar}$), 122.8 ($2C_{ar}$), 121.2 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 21.7 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{20}H_{20}N_3O_5S$: calcd. 414.1123, found 400.1125.

1,7,8-trimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-4-nitrobenzenesulfonate (13)

Yield 69 mg (89%) as an orange solid.M.p = 243-244°C.R_f= 0.4 (DCM/MeOH98:2). IR (ATR) ν_{max}(cm^{-1}) = 2960, 1260, 1082, 1020, 785.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.25 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 8.16 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.48 (s, 1H, CH_{ar}), 7.39 (s, 1H, CH_{ar}), 3.55 (t, 1H, *J* = 3.9 Hz, CH_{ar}), 3.38 (appearant t, 1H, *J* = 3.6 and 3.9 Hz, CH), 2.87 (s, 3H, CH_3), 2.44 (s, 6H, $2CH_3$), 1.79-1.74 (m, 2H, CH_2), 1.47 (t, 2H, *J* = 3.9 Hz, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.6 (C_{ar}), 152.8 (C_{ar}), 147.3 (C_{ar}), 145.9 (C_{ar}), 141.5 (C_{ar}), 139.3 (C_{ar}), 133.3 (C_{ar}), 130.6 (C_{ar}), 130.3 (C_{ar}), 126.8 (C_{ar}), 124.3 ($2C_{ar}$), 123.2 (C_{ar}), 119.3 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 20.4 (C), 20.0 (C).HRMS (ESI): $[M+H]^+$ $C_{21}H_{22}N_3O_5S$: calcd. 428.1280, found 428.1281.

General Procedure for Preparation of Methylbenzene Sulfonates (D)[13]

To a Mixture of phenol substituents (0.185 mmol, 1 eq.) in freshly distillated DCM (2 mL), triethyl amine (19 µL, 0.185 mmol, 1 eq.) p-methylbenzene sulfonyl chloride (35 mg, 0.185, 1 eq.) in DCM was added dropwise and stirred for 12h at room temperature. The solvent evaporated *in vacuo*, the residue dissolved in EtOAc and washed with 1N HCl, 1N NaOH, saturated NaCl solution. The organic phase was dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the crude material purified by chromatography on silica gel (DCM/ MeOH) to provide the expected products (**14-16**) as a yellow solid.

1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-y-4-methylbenzenesulfonate (14)

Yield 68 mg (82%) as yellow solid.M.p = 179-181°C.R_f= 0.3 (DCM/MeOH99:1). IR (ATR) ν_{max}(cm^{-1}) = 2150, 1254, 1404, 1380, 1200.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.90 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.79 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.74 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.45 (d, 1H, *J* = 4.5 Hz, CH_{ar}), 7.23 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.15 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.57 (t, 1H, *J* = 3.9 Hz, CH), 3.38 (t, 1H, *J* = 3.9 Hz, CH), 2.87 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.80-1.75 (m, 2H, CH_2), 1.51 (appear antt, 2H, *J* = 4.2 and 3.9 Hz, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.7 (C_{ar}), 152.9 (C_{ar}), 144.8 (C_{ar}), 141.3 (C_{ar}), 137.8 (C_{ar}), 131.9 (C_{ar}), 129.7 ($2C_{ar}$), 128.9 ($2C_{ar}$), 127.7 (C_{ar}), 127.3 (C_{ar}), 124.7 (C_{ar}), 124.0 (C_{ar}), 123.4 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 21.1 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{20}H_{21}N_3O_3S$: calcd. 369.1273, found 369.1273.

1,8-dimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-4-methylbenzenesulfonate (15)

Yield 62 mg (88%) as yellow solid.M.p = 203-204°C.R_f= 0.3 (DCM/MeOH99:1). IR (ATR) ν_{max}(cm^{-1}) = 2150, 1254, 1405, 1375, 1205. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.77 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.73 (d, 1H, *J* = 4.8 Hz, CH_{ar}), 7.48 (d, 1H, *J* = 0.9 Hz, CH_{ar}), 7.41 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.11 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.48 (appearant t, 1H, *J* = 3 and 6.3 Hz, CH), 3.38 (t, 1H, *J* = 3.3 Hz, CH), 2.89 (s, 3H, CH_3), 2.62 (appearant t, 2H, *J* = 3.6 and 3.3 Hz, CH_2), 2.48 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.04-1.99 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5

MHz): δ (ppm) = 154.2 (C_{ar}), 153.8 (C_{ar}), 143.6 (C_{ar}), 141.3 (C_{ar}), 140.2 (C_{ar}), 137.8 (C_{ar}), 129.7 (2C), 128.9 ($2C_{ar}$), 128.0 (C_{ar}), 126.8 (C_{ar}), 125.3 (C_{ar}), 122.8 ($2C_{ar}$), 121.2 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 21.1 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{21}H_{23}N_2O_3S$: calcd. 383.1429, found 383.14290.

1,7,8-trimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-4-methylbenzenesulfonate (16)

Yield 69 mg (89%) as white solid.M.p = 239-240°C.R_f= 0.3 (DCM/MeOH91:1). IR (ATR) ν_{max}(cm^{-1}) = 2150, 1253, 1400, 1378, 1200. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.88 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.54 (s, 1H, CH_{ar}), 7.45 (d, 2H, *J* = 4.5 Hz, CH_{ar}), 7.41 (s, 1H, CH_{ar}), 3.45 (appearant t, 2H, *J* = 3.3 and 3 Hz, CH_2), 3.08 (appearant t, 2H, *J* = 3.6 and 3.3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.44 (d, 6H, *J* = 3 Hz, $2CH_3$), 2.36 (s, 3H, CH_3), 2.00-1.96 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.6 (C_{ar}), 152.8 (C_{ar}), 141.5 (C_{ar}), 141.3 (C_{ar}), 139.3 (C_{ar}), 137.8 (C_{ar}), 133.3 (C_{ar}), 130.6 (C_{ar}), 129.7 (C_{ar}), 128.9 ($2C_{ar}$), 126.8 ($2C_{ar}$), 123.2 (C_{ar}), 119.3 (C_{ar}), 37.8 (C), 22.9 (C), 21.1 (C), 20.4 (C), 20.0 (C).HRMS (ESI): $[M+H]^+$ $C_{23}H_{28}N_2O_3S$: calcd. 412.1820, found 418.1819.

General Procedure for Preparation of Triflates (E)[14]

A mixture of pyridine (50 mg, 0.416 mmol, 2 eq.) and phenol substituents(0.208 mmol, 1 eq.) in dry DCM (5mL) at 0°C, Triflicanhyride (26 µL, 0.156 mmol, 0.75 eq.) was added then stirring for 9h at RT. In order to keep basicity of reaction (pH 13), Ammonium hydroxide solution was added and the solvent evaporated under vacuum, the residue extracted with EtOAc, then washed with brine, and dried over $MgSO_4$. After removal of the solvents, the crude was purified by chromatography on silica gel (petroleum ether/ethyl acetate) to provide the desired products (**17-19**) as a white solid.

1-methyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-trifluoromethanesulfonate (17)

Yield 60 mg (84%) as a white solid.M.p = 178-179°C.R_f= 0.35 (petroleum ether/ethyl acetate 75:25). IR (ATR) ν_{max}(cm^{-1}) = 3673, 2986, 2900, 1405, 1393, 1377, 1240, 1221, 1073, 1055. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.77-7.75 (m, 2H, CH_{ar}),7.23 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}),7.16 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.45 (appearant t, 2H, *J* = 3.3 and 3 Hz, CH_2), 3.10 (appearant t, 2H, *J* = 3.3 and 3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.01-1.97 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.7 (CF_3), 152.9 (C_{ar}), 144.8 (C_{ar}), 131.9 (C_{ar}), 127.7 (C_{ar}), 127.3 (C_{ar}), 124.7 (C_{ar}), 124.0 (C_{ar}), 123.4 (C_{ar}), 122.4 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 20.0 (C).HRMS (ESI): $[M+H]^+$ $C_{14}H_{14}F_3N_2O_3S$: calcd. 347.0677, found 347.0676.

1,8-dimethyl-1,2,3,4-tetra hydrobenzo[b][1,8] naphthyridin-5-yl tri fluoro methane sulfonate (18)

Yield 61 mg (82%) as an white solid.M.p = 160-161°C.R_f= 0.36 (petroleum ether/ethyl acetate 75:25). IR (ATR) ν_{max}(cm^{-1}) = 3673, 2986, 2901, 1404, 1377, 1239, 1072. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.63 (d, 1H, *J* = 4.5 Hz, CH_{ar}), 7.49 (d, 1H, *J* = 0.6 Hz, CH_{ar}), 7.11 (dd, 1H, *J* = 0.6 and 4.5 Hz, CH_{ar}), 3.45 (appearant t, 2H, *J* = 3.3 and 3 Hz, CH_{ar}), 3.09 (appearantt, 2H, *J* = 3.6 and 3.3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.01-1.97 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.8 (CF_3), 152.9 (C_{ar}), 143.6 (C_{ar}), 140.2 (C_{ar}), 128.0 (C_{ar}), 126.8 (C_{ar}), 125.3 (C_{ar}), 122.8 (C_{ar}),121.2 (C_{ar}), 120.3 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 20.4 (C).HRMS (ESI): $[M+H]^+$ $C_{15}H_{16}F_3N_2O_3S$: calcd. 361.0833, found 361.0832.

1,7,8-trimethyl-1,2,3,4-tetrahydrobenzo[b][1,8] naphthyridin-5-yl-trifluoromethane-sulfonate(19)

Yield 42 mg (85%) as an white solid.M.p = 186-187°C.R_f= 0.35 (petroleum ether/ethyl acetate 75:25). IR (ATR) ν_{max}(cm^{-1}) = 3673, 2986, 2900, 1404, 1379, 1235, 1219. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.43 (s, 1H, CH_{ar}), 7.40 (s, 1H, CH_{ar}), 3.45 (appearantt, 2H, *J* = 3 and 3.3 Hz, CH_2), 3.09 (appearant t, 2H, *J* = 3.6 and 3.3 Hz, CH_{ar}), 2.90 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.01-1.97 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 154.8 (CF_3), 152.8 (C_{ar}), 141.5 (C_{ar}), 139.3 (C_{ar}), 133.3 (C_{ar}), 130.6 (C_{ar}), 126.8 (C_{ar}), 120.3 (C_{ar}),119.2 (C_{ar}), 118.2 (C_{ar}), 48.6 (C), 37.8 (C), 22.9 (C), 20.4 (C), 20.0 (2C).HRMS (ESI): $[M+H]^+$ $C_{16}H_{18}F_3N_2O_3S$: calcd. 375.0990, found 375.0988.

General Procedure for Coupling Reactions (F)[15]

To a mixture of the triflate substituents (0.269 mmol, 1 eq.) in dry dioxane (5 mL), phenyl boronic acid (54 mg, 0.403 mmol, 1.5 eq.) K_3PO_4 (39 mg, 0.184 mmol, 1 eq.) was added. The reaction

mixture was bubbled for 30 min. $Pd(PPh_3)_4$ (31 mg, 0.027 mmol, 0.1 eq.) was added to the reaction and refluxed for 12h. The mixture was cooled down to room temperature and the solvent evaporated under vacuum. The product was purified by chromatography on silica gel (petroleum ether/ethyl acetate) to provide the expected products (20-22) as a white solid.

1-methyl-5-phenyl-1,2,3,4-tetrahydrobenzo [b][1,8]naphthyridine (20*)*

Yield 59 mg (80%) as white solid. M.p = 237-238°C.R_f= 0.3 (petroleum ether/ ethyl acetate 85:15). IR (ATR) ν_{max}(cm^{-1}) = 1260, 1151, 1032, 850, 732. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.83 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.59 (dd, 2H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.44 (appearant t, 2H, *J* = 4.5 and 4.2 Hz, CH_{ar}), 7.40-7.35 (m, 2H, CH_{ar}), 7.16 (td, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.09 (td, 1H, J = 0.9 and 4.5 Hz, CH_{ar}), 3.44 (t, 2H, J = 3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.72 (appearant t, 2H, *J* = 3.6 and 3.3 Hz, CH_2), 1.99-1.94 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.1 (C_{ar}), 147.4 (C_{ar}), 146.4 (C_{ar}), 139.5 (C_{ar}), 129.9 ($2C_{ar}$), 129.0 (C_{ar}), 128.6 ($2C_{ar}$), 128.0 (C_{ar}), 127.6 (C_{ar}), 126.6 ($2C_{ar}$), 125.6 (C_{ar}), 124.3 (C_{ar}), 124.2 (C_{ar}),48.6 (C), 37.8 (C), 25.2 (C), 22.9 (C).HRMS (ESI): $[M+H]^+$ $C_{19}H_{19}N_2$: calcd. 275.1548, found 275.1548.

1,8-dimethyl-5-phenyl-1,2,3,4-tetrahydrobenzo [b][1,8]naphthyridine (21)

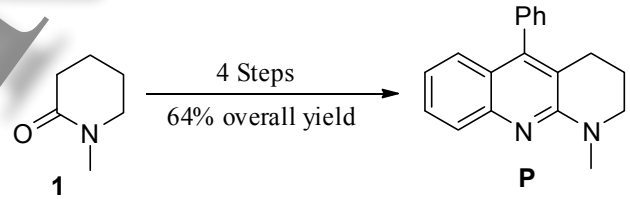
Yield 64 mg (83%) as white solid.M.p = 243-245°C.R_f= 0.33 (petroleum ether/ ethyl acetate 85:15). IR (ATR) ν_{max} (cm^{-1}) = 1260, 1151, 1035, 856, 730. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.59 (dd, 2H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 7.56 (d, 1H, *J* = 0.9 Hz, CH_{ar}), 7.44 (appearant t, 2H, *J* = 4.5 and 4.2 Hz, CH_{ar}), 7.38-7.35 (m, 1H, CH_{ar}), 7.26 (d, 1H, *J* = 4.5 Hz, CH_{ar}), 7.04 (dd, 1H, *J* = 0.9 and 4.5 Hz, CH_{ar}), 3.44 (t, 2H, *J* = 3.3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.71 (t, 2H, *J* = 3.6 Hz, CH_2), 2.42 (s, 3H, CH_3), 1.99-1.94 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 155.8 (C_{ar}), 146.3 (C_{ar}), 140.9 (C_{ar}), 139.5 (C_{ar}), 129.9 ($2C_{ar}$), 128.7 (C_{ar}), 128.6 ($2C_{ar}$), 127.6 (C_{ar}), 127.5 (C_{ar}), 126.8 (C_{ar}), 124.6 (C_{ar}), 122.8 (C_{ar}), 48.6 (C), 37.8 (C), 25.2 (C), 22.9 (C), 21.7 (C).HRMS (ESI): $[M+H]^+$ $C_{20}H_{21}N_2$: calcd. 289.1704, found 289.1705.

1,7,8-trimethyl-5-phenyl-1,2,3,4-tetrahydrobenzo [b] [1,8]naphthyridine(22)

Yield 66 mg (81%) as white solid.M.p = 237-238°C.R_f= 0.3 (petroleum ether/ ethyl acetate 85:15). IR (ATR) ν_{max}(cm^{-1}) = 1261, 1153, 1033, 850, 735. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.59 (dd, 1H, J = 0.9 and 4.5 Hz, CH_{ar}), 7.47-7.35 (m, 4H, CH_{ar}), 7.05 (s, 1H, CH_{ar}), 3.44 (appearant t, 2H, *J* = 3 and 3.3 Hz, CH_2), 2.90 (s, 3H, CH_3), 2.71 (t, 2H, *J* = 3.6 Hz, CH_2), 2.43 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.99-1.94 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 155.0 (C_{ar}), 147.3 (C_{ar}), 143.6 (C_{ar}), 140.6 (C_{ar}), 139.5 (C_{ar}), 133.7 (C_{ar}), 129.9 ($2C_{ar}$), 129.5 (C_{ar}), 128.6 ($2C_{ar}$), 127.6 ($2C_{ar}$), 127.2 (C_{ar}), 124.7 (C_{ar}), 124.0 (C_{ar}),48.6 (C), 37.8 (C), 25.2 (C), 22.9 (C), 20.0 (C).HRMS (ESI): $[M+H]^+$ $C_{21}H_{23}N_2$: calcd. 303.1861, found 303.1861.

RESULT AND DISCUSSION

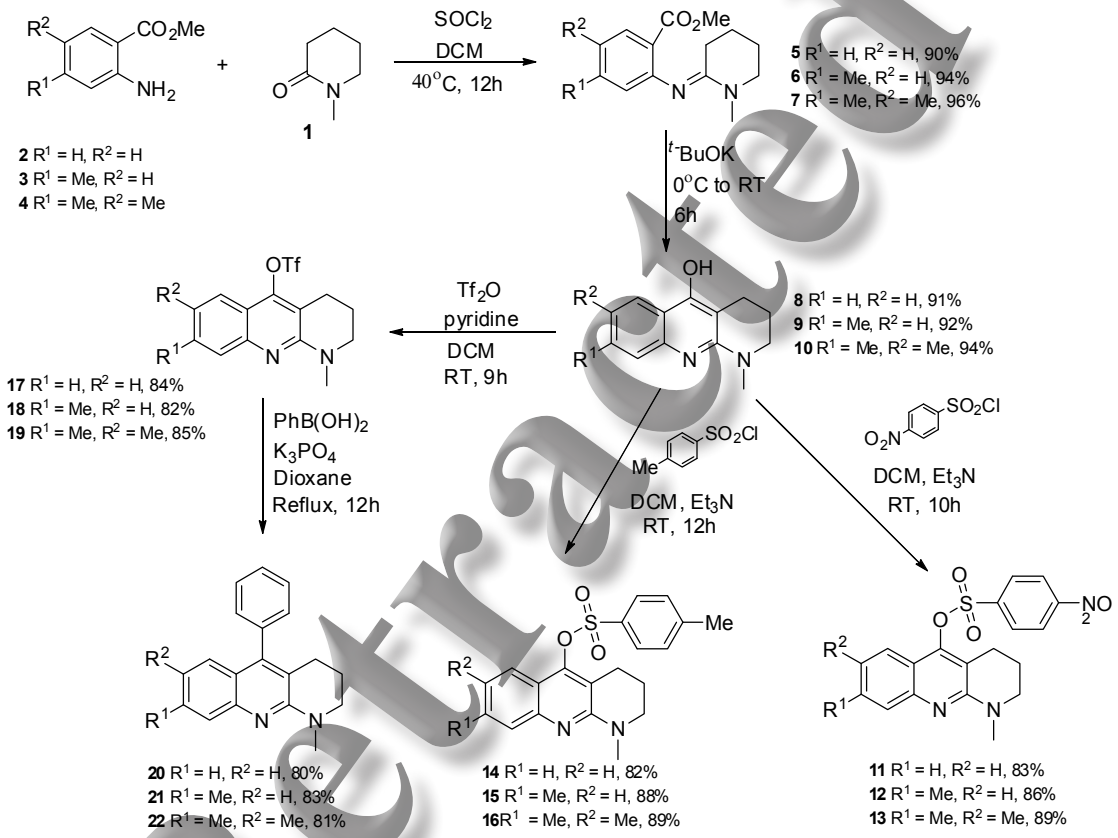
The preliminary studies of the synthesis of Naphthyridine models(only in four steps and yield 64%)Scheme 1which can give approach toward total synthesis of the natural products such as Leucophyllidine starting from the simple cyclic amide (2-piperidinone) 1.



Scheme 1: Synthesis of Tricyclic Hetero-compound model

In this project, we described the synthesis of tricyclic heterocyclic benzo Naphthyridine compounds as a models. These derivatives could exhibit important pharmacological properties, such as anticancer activity. The strategy **Scheme 2** of this reaction starts with successful Friedlander type annulation between substituted aniline **2**, **3**, **4** and piperidinone**1** using thionyl chloride. Furthermore,

the intramolecular cyclization process of the resulting amidines **5**, **6** and **7** was applied, which in treatment with *t*-BuOK led to the desired phenol products **8**, **9** and **10** in high yields. Transformation of the hydroxyl group into the corresponding tetrahydrobenzo nitro compounds **11**, **12**, **13**and methylbenzene sulfonate compounds **14**, **15** and **16** through reaction with p-nitro- and p-methylsulfonyl chloride or triflate compounds **17**, **18** and **19** were reported to be a very efficient processes. Palladium-catalyzed[16-18]cross-coupling between triflate compounds and phenyl boronic acid following a Suzuki reaction[19-20]provided the desired products **20**, **21** and **22** in very good yields.



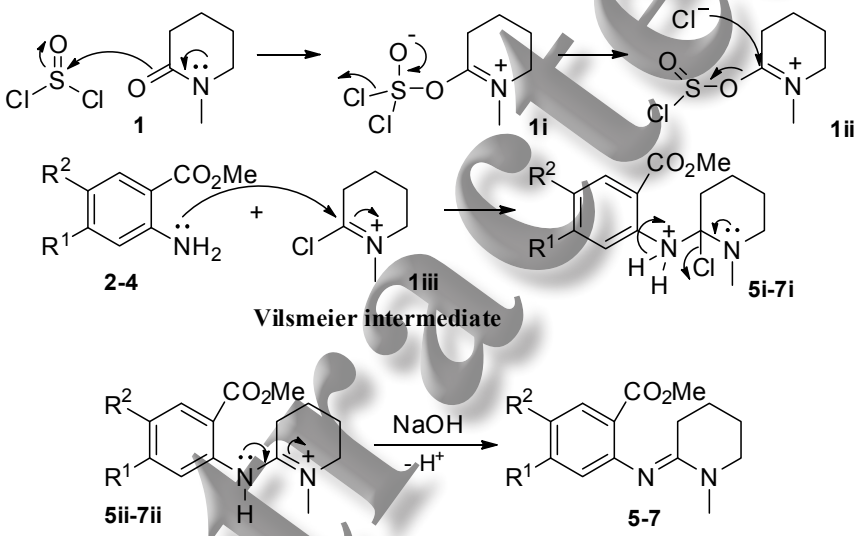
Scheme 2: Preparation of Tricyclic Naphthyridine models through Nosylation, Methylation and Suzuki-coupling reactions

The mechanism of commercially available 1-methylpiperidin-2-one**1** with aniline substituents **2**, **3** and **4** can involves through attack of the amide carbonyl group onto $SOCl_2$ to generate **1i**, and a chloride anion which can re-attack the C=N bond in and give Vilsmeier intermediate **1ii**. The Vilsmeier reagent is an efficient, economical and mild reagent for the formulation of reactive aromatic and hetero-aromatic substrates. It is now used as a powerful synthetic tool for many constructions of many heterocyclic compounds[21-23]. The products **5**, **6** and **7** can obtain after nucleophilic substitution reaction through work up with basic conditions Scheme 3.

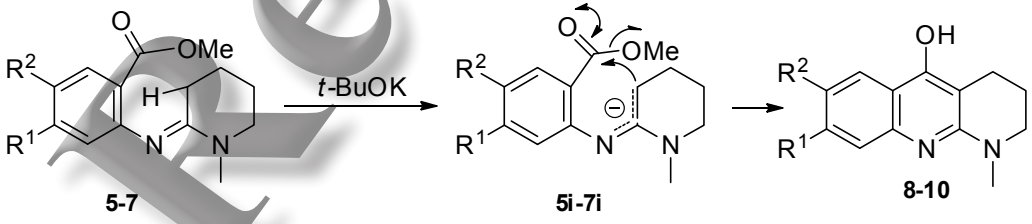
Subsequently, the proposed mechanism for the described transformation of amidines **5**, **6** and **7** is outlined in Scheme 4 which involves the preliminary abstract proton by *t*-BuOK as a strong base. We believe that the anion is stable at 0°C, however at temperature at room temperature at it undergo elimination of the ester group and aromatization to afford the phenol tricyclic products **8**, **9** and **10** Scheme 4.

Furthermore, converting the phenol to the triflate compounds can proceed through the mechanism starting through attack of the hydroxyl group onto the anhydride Tf_2O compound and generate **17i-19i**, which can then undergo deprotonation using base such as trimethylamine in presence of DMAP as a catalyst and produce the expected products **17-19 Scheme 5.**

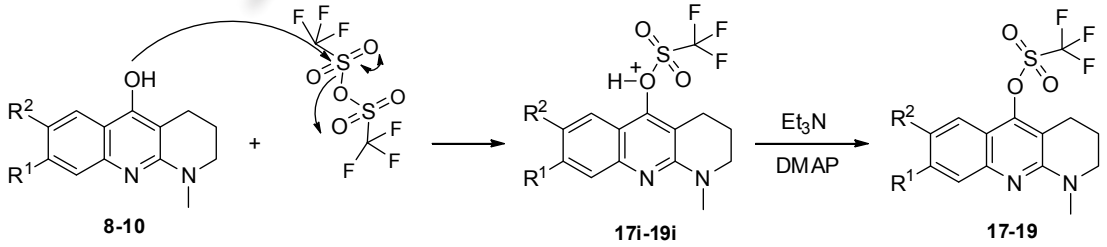
Finally, a general mechanism for the Suzuki reaction cross-coupling process of triflate compounds **17-19** with palladium (0) as a catalyst normally involves three steps starting with oxidative addition[24] of triflate to the Pd (0) complex and organopalladiumtriflate**17-19**. While the second step includes transmetallation[25-27] with phenyl boronic acid to produce diorganopalladium complex **20i-22i**. This complex undergoes a reductive elimination[28] to give and form a new carbon-carbon bond in the final products **20-22 Scheme 6**.



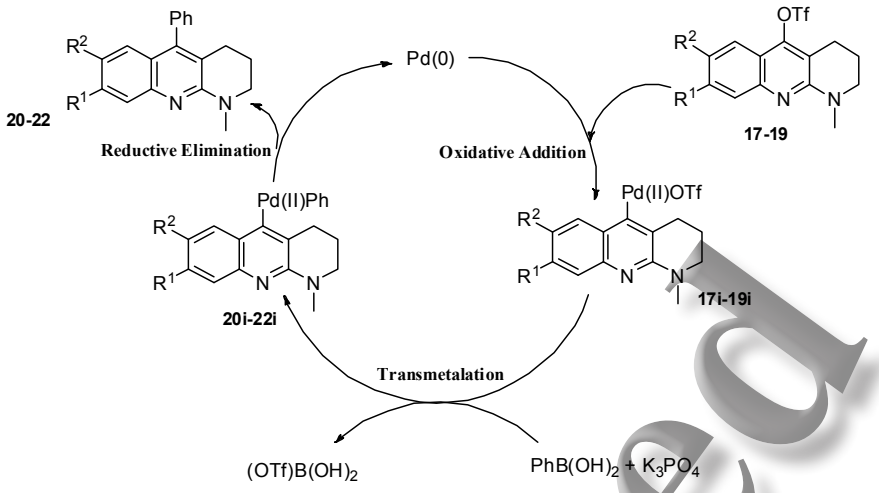
Scheme 3: Proposed mechanism for the formation of amidine products 5, 6 and 7



Scheme 4: Mechanism of the transformation of amidine to the corresponding phenols



Scheme 5: Mechanism of the preparation of Triflates in presence of base



Scheme 6: Final mechanism suzuki-coupling reaction of Triflate compounds in presence of Pd (0) catalyst

CONCLUSION

In summary, we have reported an efficient scope toward the fused tricyclic heterocyclic benzo Naphthyridine, based on the formation of an amidine key which prepared through the Vlismeier intermediate, followed by cyclization process via installing the hydroxyl group to provide the phenol compounds. Transformation of the hydroxyl group into the corresponding tetrahydrobenzo nitro compounds and methyl benzene sulfonate or a triflate compounds allowed to final Suzuki reaction to be carried out in the presence of a phenyl boronic acid, furnishing the desired products in good overall yield (64% over all yield in 4 steps from the commercially available methyl piperidinone.

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