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Novel synthetic route of aryl-aminopyrazine

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Abstract—We report a novel synthetic route of aryl-aminopyrazine through a new cyclization reaction by using a hydroxylamine. Starting from Boc-glycine and aminonitrile, the aminopyrazine ring was prepared in several steps. After trifluoromethane sulfonylation of the aminopyrazinone, the resultant triflate was subjected to Suzuki–Miyaura coupling reaction with aryl boronic acid to afford coelenteramine.

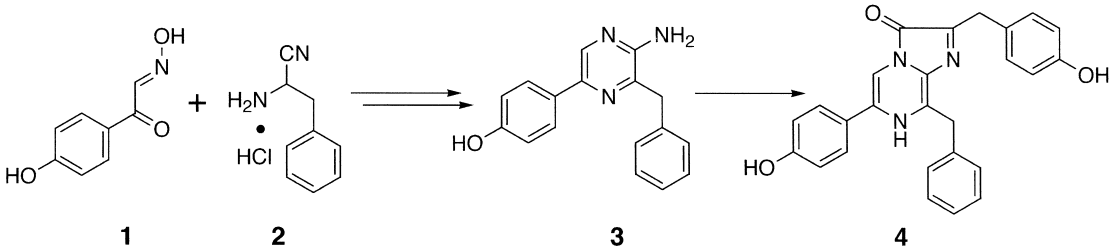
1. Introduction

Kishi and Goto established the synthetic route of coelenterazine (**4**) from coelenteramine (**3**) as a precursor, which was prepared from the condensation of keto-oxime (**1**) and aminonitrile (**2**) (Scheme 1).[1] This has been so far the only promised method for the synthesis of benzyl-aryl-aminopyrazines. Aminopyrazines are spread over many natural products, especially in luminous marine organisms like jellyfish (*Aequorea aequorea*),[2] fireflysquid (*Watasenia scintillans*),[3] and flyingsquid Tobiika (*Symplectoteuthis oualaniensis* L.),[4] etc. Their luciferin has imidazopyrazinone ring structure (**4**) that has been synthesized from aminopyrazine (Scheme 1). Since it is difficult to get many kinds of keto-oximes, it has been requested to develop alternative routes accessible to the various aryl-aminopyrazine analogs. And such methods would encourage those who study on those luminous creatures. Nakamura reported another synthetic way for coelenteramine (**3**) of great value for these reasons,[5] but their synthetic method needs 2-aminopyrazine as a starting material. They use Stille coupling reaction with tin reagents having toxicity and enforcing the tedious process in waste of the tin reagents. Therefore, we aimed at new synthetic route of aminopyrazine derivatives, starting from *N*-Boc-glycine (**8**) and aminonitrile hydrochloride (**2**), and we planned to make a 5-aminopyrazine-2-*O*-triflate (**6**) as the coupling partner for the coelenteramine synthesis. After getting 2-*O*-trifluoromethanesulfonyl-5-aminopyrazine (**6**), Suzuki–Miyaura coupling[6] reaction would enable us to synthesize various aminopyrazine analogs.

2. Results and discussion

2.1. Synthetic plan

During the research of molecular mechanism of symplectin (a photoprotein of *Symplectoteuthis oualaniensis* L.),[7] we focused on the protein structure of symplectin active site where dehydrocoelenterazine (**5**) binds.[8] Due to the limitation of the availability of variation of acetophenone



Scheme 1. Synthetic route of coelenterazine (**4**) from coelenteramine (**3**) by Kishi and Goto.[1]

Keywords: Aminopyrazine; Suzuki coupling; Hydroxylamine.
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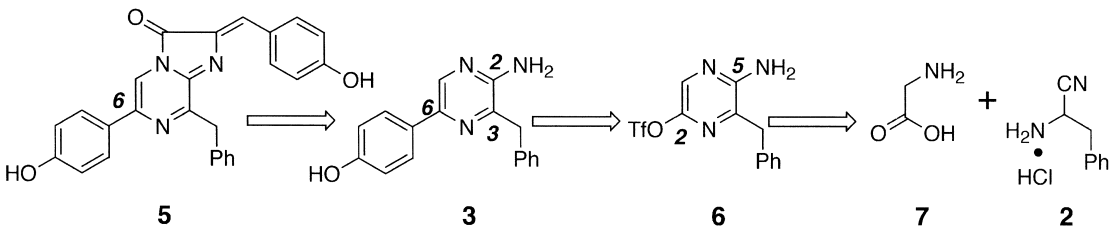
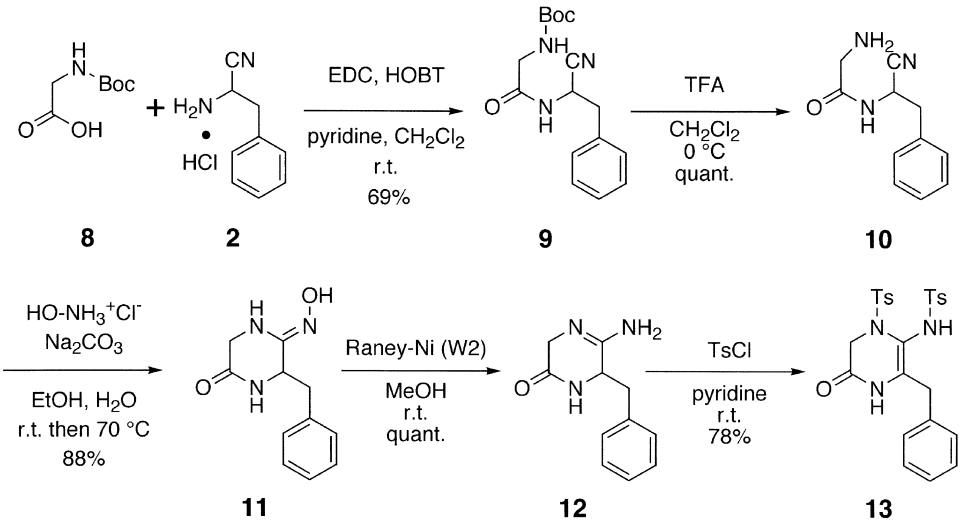
as a photoprobe, we could not modify the aromatic ring in 6-position of dehydrocoelenterazine for photoaffinity labeling experiments. Therefore, we planned to make the novel route for the synthesis of dehydrocoelenterazine having various functions at the 6-position and to devise a new synthetic route of aminopyrazine. Considering the Suzuki–Miyaura coupling as the final functionalization of aminopyrazine, we retrosynthesized dehydrocoelenterazine (**5**) as shown in Scheme 2. Since dehydrocoelenterazine (**5**) is derived from coelenteramine (**3**), we must devise a synthetic route of the triflate (**6**). We thought that the triflate (**6**) must be derived from glycine (**7**) and aminonitrile hydrochloride (**2**). Therefore, we started our synthesis from commercially available *N*-Boc-glycine (**8**) and aminonitrile hydrochloride (**2**).

2.2. Synthetic route

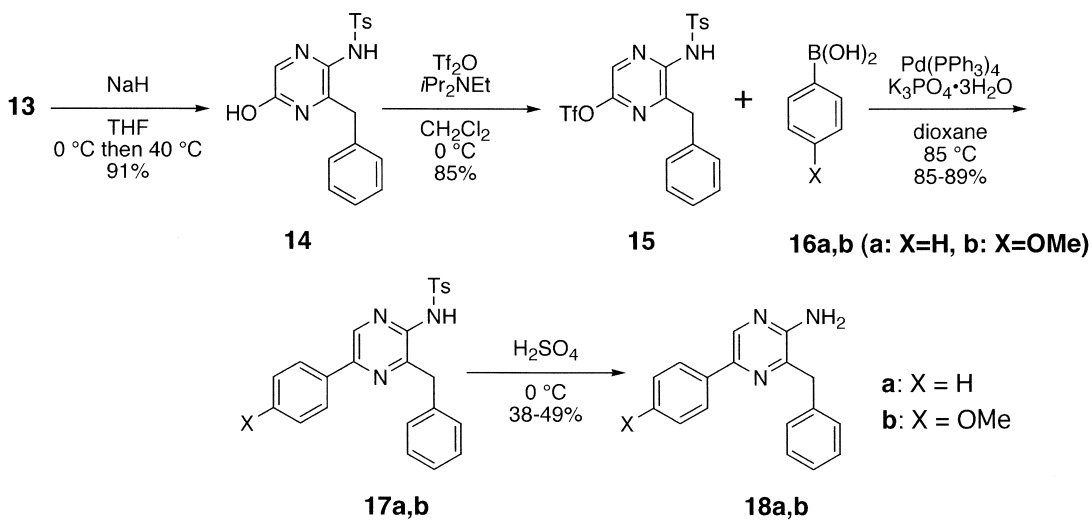
Schemes 3 and 4 show our novel synthetic route of the synthesis of triflate (**6**). Condensation of *N*-Boc-glycine (**8**) and aminonitrile hydrochloride (**2**) with EDC (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide), HOBt



Scheme 2. Synthetic plan of dehydrocoelenterazine (**5**) from aminopyrazine triflate (**6**).



Scheme 3. Synthetic route for the formation of pyrazine core (**11**) by using the key reaction of hydroxyamine from Boc-glycine (**8**) and aminonitrile (**2**).



Scheme 4. Synthetic route for aminopyrazine (**18a**,**b**) by using triflate **15** as key intermediate.

(hydroxybenzotriazole) and pyridine in dichloromethane afforded the amide (**9**) in 69% yield.

Isolation of amide (**9**) was turned out to be much easier than the condensation by using DIC (diisopropylcarbodiimide), since the urea produced from EDC was water soluble and easily removed with acidic water. The Boc protecting group of amide (**9**) was favorably removed by treatment with trifluoroacetic acid to give amidoaminonitrile (**10**) as a white powder in quantitative yield. Unfortunately, the direct cyclization of **10** to cyclic amidine (**12**) was failed after many trials, probably due to the weak nucleophilicity of primary amine in the substrate (**10**). The subsequent cyclization of amide-aminonitrile (**10**) with hydroxylamine was the key step in this synthetic route to afford cyclic oxime (**11**). It must be noted that stirring the reaction mixture at room temperature over night should be followed at 70 °C for 3 h for obtaining cyclized product in high yield. On the other hand, stirring the reaction mixture at 70 °C for 3 h from the beginning gave the cyclic oxime (**11**) in low yield. Hydrogenolysis of the oxime (**11**) was accomplished with hydrogen under atmospheric pressure in methanol and Raney nickel (W-2) as catalyst. Due to the insolubility of the amidine (**12**) in many organic solvents, the protection of amidine (**12**) was proved to be unsuccessful. However, by using pyridine as the sole solvent, tosylation of the amidine (**12**) successfully afforded ditosylate (**13**) in 78% yield. We found the double bond migration of the ditosylate (**13**) from the amidine (**12**), and we confirmed the protected position of amine in **13** with two dimensional NMR analyses. The removal of one of the tosyl groups in **13** with sodium hydride in THF followed by recrystallization afforded aromatized hydroxypyrazine (**14**) as yellow needles in 91% yield. Hydroxypyrazine (**14**) was converted to triflate (**15**) with trifluoromethanesulfonic anhydride and *N*,*N*-diisopropylethylamine as a base in dichloromethane. This triflate (**15**) was the precursor of various aminopyrazine analogs by using Suzuki–Miyaura coupling. In this report, we selected both phenylboronic acid (**16a**) and 4-methoxyphenylboronic acid (**16b**) as coupling partners. Following the procedure established by Suzuki,[9] triflate (**15**) was coupled with boronic acids (**16a**,**b**) by using $Pd(PPh_3)_4$ and K_3PO_4 to afford *N*-tosylamidepyrazine (**17a**,**b**) in 85–89% yield. The removal of tosyl group in *N*-tosylamidepyrazine (**17a**,**b**) was accomplished by treatment with conc. H_2SO_4 at 0 °C to provide target aminopyrazine (**18a**,**b**) as a white solid in 38–49% yield. In the case of **18b**, the spectroscopic data was identical with the data of aminopyrazine that was synthesized by using Kishi and Goto route.[10] Although we purified each compound in each step for the spectroscopic analysis, we noted here that it is also possible to obtain hydroxyaminopyrazine (**14**) in 46% yield in 5 steps without any purification process starting from *N*-Boc-amide (**9**). Although 5 steps-yield was decreased probably due to the impurities of each starting material, omission of each purification process is more convenient for the preparation of 2-hydroxy-5-aminopyrazine (**14**).

3. Summary

We succeeded in developing up the novel synthetic route of aminopyrazine by using these synthetic route reported herein. This method should enable us to prepare many kinds of aminopyrazine analogs, which have potentiality many functions at the 6-position in coelenteramine through Suzuki–Miyaura coupling of triflate (**15**) with a variety of boronic acid. Furthermore, the merit of the use of Suzuki–Miyaura coupling is the convenience of boron reagents compare to the tin reagents for Stille coupling. Further progress of the current synthesis and the corresponding luminescent activity is to be published elsewhere.

4. Experimental

4.1. General

All melting points were measured on Yanaco MP-S3 and uncorrected. IR spectra were recorded on a PERKIN ELMER Paragon 1000 FT-IR spectrophotometer. Proton NMR spectra were recorded on a JEOL GSX 270 for 270 MHz, a Varian Gemini-2000 for 300 MHz, a JEOL JNML-500 for 500 MHz or a Bruker AMX-600 for 600 MHz. Chemical shift (δ) are given in parts per million relative to tetramethylsilane (δ 0.00) or CD_3OD (δ 3.30) or DMSO-d_6 (δ 2.49) as internal standard. Coupling constants (*J*) are given in Hz. Carbon NMR were recorded on a JEOL GSX 270 for 67.8 Hz, or on a Varian Gemini-2000 for 75 MHz, or on a JEOL JNML-500 for 125.7 Hz, or on a Bruker AMX-600 for 150.9 MHz. Chemical shifts are (δ) given in parts per million relative to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0) or DMSO-d_6 (δ 45.0) as internal standard. Coupling constants (*J*) are given in Hz. Low-resolution EI mass spectra and FAB mass spectra were measured with a JEOL JMS-700 or JMS-600. High-resolution (HR) mass spectra were measured with a JEOL JMS-700. Elemental analysis and HRMS were performed by Analytical Laboratory of this school. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Tetrahydrofuran (THF) and 1,4-dioxane were distilled from sodium metal in the presence of sodium benzophenone ketyl as indicator. Pyridine was dried over NaOH pellet and used without distillation. The other solvents were of reagent grade. Analytical thin-layer chromatography (tlc) was conducted on precoated tlc plates: silica gel 60 F-254 [E.Merck (Art 5715) Darmstadt, Germany], layer thickness 0.25 mm. Silica gel column chromatography utilized Silica Gel 60 (spherical) 40–50 μm [KANTO CHEMICAL CO., INC].

4.1.1. Boc-amidenitrile (9). To a solution of *N*-Boc-glycine (**8**) (5.00 g, 28.6 mmol) and aminonitrile hydrochloride (**2**) (5.49 g, 30.0 mmol, 1.1 equiv.) in CH_2Cl_2 (70 ml) and pyridine (20 ml) was added hydroxybenzotriazole (4.24 g, 31.4 mmol, 1.1 equiv.) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (6.03 g, 31.4 mmol, 1.1 equiv.) at 0 °C in an ice bath under Ar atmosphere. This mixture was stirred for 15 h at room temperature. The urea was removed by washing with 1 N HCl aq, then the reaction mixture was washed with water, saturated $NaHCO_3$ and diluted brine. Purification by column chromatography on silica gel with AcOEt/hexane (1:1) provided amide (**9**) (6.00 g, 69% yield) as a yellow curdy solid.

Compound **9**: mp 85–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s, *t*-Bu), 3.10–3.07 (2H, m, benzyl), 3.77 (1H, dd,

J=16.8, 5.7 Hz, C(O)CH_2NH), 3.81 (1H, dd, J=16.8, 4.8 Hz, C(O)CH_2NH), 5.11 (1H, ddd, J=15.0, 6.9, 6.9 Hz, CNCH), 5.29 (1H, brd, BocNH), 7.14 (1H, brd, amide-NH), 7.38–7.25 (5H, m, Ph) ppm. ^{13}C NMR (75 MHz) δ 28.3, 37.4, 42.6, 43.0, 78.3, 119.2, 127.4, 128.6, 129.6, 135.8, 156.0, 169.8 ppm. IR (KBr): 3335, 2957, 1679, 1533, 1208, 1127 cm^{-1}. FAB-MS (NBA) m/z 304 (MH$^+$). Anal. calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.10; H, 7.05; N, 13.81.

4.1.2. Amidenitrile TFA salt (10). To a solution of **9** (19.5 g, 64.3 mmol) in 60 ml of CH_2Cl_2 was added trifluoroacetic acid (60 ml) at 0 °C under nitrogen. After stirring for 1.5 h at 0 °C, this mixture was quenched with ice and was evaporated to remove the solvents. Resulting white solid was TFA salt (**10**) (20.4 g, quantitative yield).

Compound **10**: mp 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17–3.05 (2H, m, benzyl), 3.35 (2H, s, C(O)CH_2NH), 5.18–5.11 (1H, dd, J=6.6, 6.9 Hz, CNCH) 7.40–7.27 (5H, m, Ph) 7.85 (1H, d, J=7.8 Hz, amide-NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.8, 41.0, 44.2, 118.1, 127.9, 128.9, 129.4, 134.4, 172.3 ppm. IR (KBr): 3335, 2960, 1678, 1532, 1209, 1126 cm^{-1}. EI-MS m/z 203 (M$^+$). Anal. calcd for $C_{13}H_{14}N_3O_3F_3$:C, 49.21; H, 4.45; N, 13.25. Found: C, 49.21; H, 4.63; N, 13.18.

4.1.3. Cyclic oxime (11). To a solution of HCl·NH_2OH (458 mg, 6.59 mmol, 2.0 equiv.) and Na_2CO_3 (350 mg, 3.30 mmol, 1.0 equiv.) in EtOH (5 ml) and water (5 ml) was added compound **10** (1.05 g, 3.30 mmol) at room temperature under Ar. After stirring for 16 h at room temperature, the reaction mixture was brought up to 70 °C, and then was continued to stir for 3 h. After evaporated the solvents, the obtained residue was dissolved in AcOEt–water and was extracted with AcOEt (5X). Resulted organic layer was dried over Na_2SO_4, and was evaporated to afford oxime (**11**) as a white solid (633 mg, 88% yield).

Compound **11**: mp 200–203 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.91 (2H, d, J=6.3 Hz, benzyl), 3.12 (1H, dd, J=23.4, 1.5 Hz, C (O) CH_2NH), 3.34 (1H, dd, J=23.4, 3.6 Hz, C(O)CH_2NH), 3.98 (1H, broad d, J=4.5 Hz, CNCH), 6.26 (1H, br, NH), 7.29–7.149 (5H, m, Ph), 8.07 (1H, d, J=3.6 Hz amide-NH), 9.10 (1H, d, J=1.5 Hz, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.8, 44.4, 52.2, 126.8, 128.4, 130.1, 137.1, 148.3, 169.0 ppm. IR (KBr): 3221, 1665, 1439, 1316,1087, 701 cm^{-1}. EI-MS m/z 219 (M$^+$). Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.26; H, 5.80; N, 18.91.

4.1.4. Cyclic amidine (12). In a 300 ml round shaped flask, Raney-Ni W2 (about 2 g, ethanol wet) and MeOH (50 ml) were charged with Ar. To this suspension was added a solution of oxime (**11**) (3.50 g, 16.0 mmol) in MeOH (100 ml), then the flask was changed with hydrogen from Ar. After stirring for 3 h at room temperature, the reaction mixture was filtered through a pad of Celite washing with MeOH. Evaporation of the resultant solution afforded pale yellow solid (**12**) (3.34 g, quantitative yield).

Compound **12**: mp 220 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (1H, dt, J=19.8, 1.7 Hz, C(O)CH_2N), 2.81 (1H, dd, J=13.5, 4.5 Hz, benzyl), 2.98 (1H, dd, J=13.5, 5.4 Hz, benzyl), 3.25 (1H, d, J=19.8 Hz, C(O)CH_2NH), 4.08 (1H, brd, Bn-CH), 5.83 (2H, br, NH_2), 7.13–7.25 (5H, m, Ph), 7.82 (1H, brd amide-NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 40.2, 49.6, 53.5, 126.9, 128.2, 130.3, 136.7, 157.3, 169.9 ppm. IR (KBr): 3425, 3192, 3032, 2742, 1681, 1329, 708 cm^{-1}. FAB-MS (NBA) m/z 204 (MH$^+$). Anal. calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.02; H, 6.61; N, 20.61.

4.1.5. Cyclic amidine ditosylamide (13). To a solution of amidine (**12**) (256 mg, 1.26 mmol) in pyridine (5 ml) was added *p*-toluenesulfonyl chloride (1.19 g, 6.26 mmol, 5.0 equiv.) at 0 °C under Ar atmosphere. This mixture was stirred for 1 h at room temperature. Pyridine was removed by diluting with toluene and concentrating in vacuo. The resulting residue was dissolved in CH_2Cl_2–water and was extracted with CH_2Cl_2 (X3). The combined organic layer was washed with brine and was dried over Na_2SO_4. After evaporated the crude product was purified by column chromatography on silica gel with AcOEt–hexane (1:1), Concentration of the solution afforded pale yellow solid (**13**) (499 mg, 78% yield).

Compound **13**: mp 87–92 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.31 (3H, s, Ts), 2.36 (3H, s, Ts), 3.29 (2H, s, benzyl), 3.91 (2H, s, C (O) CH_2), 7.12 (2H, d, J=7.9 Hz, Ts), 7.18–7.26 (5H, m, Ph), 7.31 (2H, d, J=8.2 Hz, Ts), 7.49 (2H, d, J=7.9 Hz, Ts), 7.74 (2H, d, J=8.2 Hz, Ts), 9.26 (1H, s, amide-NH), 9.48 (1H, s, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.9, 21.0, 33.3, 49.5, 110.7, 126.3, 126.9, 127.9, 128.4, 128.8, 129.2, 129.4, 133.4, 133.9, 136.4, 138.4, 142.6, 144.0, 164.9 ppm. IR (KBr): 3271, 2959, 1672, 1511, 1378, 1217 cm^{-1}. FAB-MS (NBA) m/z 287 (MH$^+$). Anal. calcd for $C_{25}H_{25}N_3O_5S_2$:C, 58.69; H, 4.93; N, 8.21. Found: C, 58.58; H, 5.05; N, 8.12.

4.1.6. 5-*N*-Tosylamide-2-hydroxypyrazine (14). To a solution of di-Ts-amidine (**13**) (102 mg, 0.20 mmol) in THF (4 ml), was added NaH (60% in mineral oil, 24.0 mg, 0.6 mmol, 3.0 equiv.) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with some drops of MeOH and was evaporated. The resulting residue was dissolved in AcOEt–water, and was extracted with AcOEt (X5). The organic layer was dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel with AcOEt–hexane (3:1) to give 5-*N*-tosylamide-2-hydroxypyrazine (**14**) as a white solid (64.5 mg, 91% yield).

Compound **14**: mp 228 °C (decomposed). FL (MeOH) Em. 435 nm (Ex. 350 nm). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.37 (3H, s, Ts), 3.30 (1H, s, OH), 4.03 (2H, s, benzyl), 7.19–7.30 (5H, m, Ph), 7.34 (2H, d, J=8.3 Hz, Ts), 7.56 (1H, s, C (OH) CH), 7.65 (2H, d, J=8.3 Hz, Ts), 9.86 (1H, s, NHTs) ppm. ^{13}C NMR (125 MHz, DMSO-d_6)[11] δ 20.9, 126.4, 126.9, 128.4, 128.7, 129.3, 138.4, 142.7 ppm. IR (KBr): 3424, 3244, 1672, 1336, 1164, 693 cm^{-1}. FAB-MS (NBA) m/z 356 (MH$^+$). HRMS (EI) calcd for $C_{18}H_{17}N_3O_3S$ 355.0991, found 355.1018 (M$^+$). Anal. calcd for $C_{18}H_{17}N_3O_3S$:C, 60.83; H, 4.82; N, 11.82. Found: C, 60.84; H, 4.79; N, 11.77.

4.1.7. 5-*N*-(*p*-Toluenesulfonyl)amide-6-benzyl-2-*O*-trifluoromethanesulfonyloxy-pyrazine (15). To a solution of 5-*N*-Ts-amide-2-hydroxypyrazine (**14**) (222 mg, 0.625 mmol) in CH_2Cl_2 (10 ml) and *i*-Pr_2NEt (300 μl, 1.74 mmol, 2.8 equiv.) was added trifluoromethansulfonic anhydride (147 μl, 0.875 mmol, 1.4 equiv.) at 0 °C under Ar atmosphere. After stirring for 2 h at 0 °C, ice water was added to the reaction mixture. This mixture was extracted with CH_2Cl_2 (X3). The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The resulting residue was purified by column chromatography on silica gel with AcOEt–hexane (1:3) to give orange solid (**15**) (259 mg, 85% yield).

Compound **15**: mp 141–143 °C. FL (MeOH) Em. 419 nm (Ex. 350 nm). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s, Ts), 4.15 (2H, s, benzyl), 7.39–7.17 (7H, m, Ph+Ts), 7.70 (2H, d, *J*=8.6 Hz, Ts), 8.06 (1H, s, CH-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 39.8, 128.0, 128.4, 128.7, 129.5, 132.5, 134.4, 135.7, 142.5, 144.8, 145.9, 147.5 ppm. IR (KBr): 3424, 2926, 1604, 1431, 1219, 1163 cm^{-1}. EI-MS *m/z* 487 (M+). Anal. calcd for $C_{19}H_{16}F_3N_3O_5S_2$:C, 46.81; H, 3.31; N, 8.62. Found: C, 46.80; H, 3.26; N, 8.48.

4.1.8. 2-*N*-(*p*-Toluenesulfonyl)amide-3-benzyl-5-phenylpyrazine (17a). A mixture of triflate (**15**) (25.0 mg, 0.051 mmol) and phenylboronic acid (**16a**) (9.4 mg, 0.077 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (5.8 mg, 0.0051 mmol, 0.1 equiv.) and $K_3PO_4{\cdot}3H_2O$ (20.5 mg, 0.077 mmol, 1.5 equiv.) in dioxane (1 ml) was heated to 80 °C for 1.5 h. The mixture was diluted with toluene (2 ml) and treated with aqueous 3 M NaOH (3 drops) and 30% H_2O_2 (3 drops) for 1 h at room temperature to oxidize the residual borane. The product was extracted with ether (X3), and dried over Na_2SO_4. After evaporated, the residue was purified by column chromatography on silica gel with AcOEt–hexane (1:3) to give **17a** as a pale yellow solid (17.9 mg, 85% yield).

Compound **17a**: mp 167–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (3H, s, Ts), 4.27 (2H, s, benzyl), 6.92 (1H, s, TsNH), 7.48–7.20 (10H, m, 2Ph+Ts), 7.70 (2H, d, *J*=8.3 Hz, Ts), 7.93 (2H, d, *J*=7.1 Hz, Ph), 8.53 (1H, s, CH-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 40.8, 126.3, 127.6, 128.3, 128.7, 129.0, 129.3, 129.5, 136.0, 137.3, 143.4, 144.2, 144.6, 146.8 ppm. IR (KBr): 3450, 1586, 1452, 1167, 1088, 695 cm^{-1}. FAB-MS (NBA) *m/z* 416 (MH^+). HRMS (FAB/NBA) calcd for $C_{24}H_{22}N_3O_2S$ 416.1433, found 416.1435 (MH^+). Anal. calcd for $C_{24}H_{21}N_3O_2S$:C, 69.37; H, 5.09; N, 10.11. Found: C, 69.37; H, 5.21; N, 9.99.

4.1.9. 2-Amino-3-benzyl-5-phenylpyrazine (18a). *N*-Ts-amidepyrazine (**17a**) (62.9 mg, 0.15 mmol) was dissolved in 1.0 ml of conc. H_2SO_4 at 0 °C in an ice bath. After stirring for 10 min at 0 °C, ice was poured into the reaction. It was extracted with AcOEt (X3), and the organic layer was washed with brine once. After neutralization with $NaHCO_3$, the organic layer was dried over Na_2SO_4. Purification by preparative TLC provided aminopyrazine (**18a**) (14.9 mg, 38% yield) as a yellow solid.

Compound **18a**: mp 133–136 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 (2H, s, benzyl), 4.46 (2H, s, amine-NH_2), 7.25–7.34 (5H, m, Ph), 7.37 (1H, dt, *J*=7.3, 1.2 Hz, Ph), 7.46 (2H, t, *J*=8.2, 7.3 Hz, Ph), 7.95 (2H, dd, *J*=8.2, 1.2 Hz, Ph), 8.39 (1H, s, Py) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 41.3, 125.2, 126.3, 128.2, 128.3, 128.4, 128.5, 128.6, 129.3, 129.5, 136.8, 137.2, 138.0, 151.7 ppm. FAB-MS (NBA): *m/z* 262 (MH^+). HRMS (FAB/NBA) calcd for $C_{17}H_{16}N_3$ 262.1344, found 262.1357 (MH^+). Anal. calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.33; H, 5.77; N, 16.01.

4.1.10. 2-*N*-(*p*-Toluenesulfonyl)amide-3-benzyl-5-(4-methoxyphenyl)pyrazine (17b). To a solution of triflate (**15**) (14.2 mg, 0.029 mmol) and boronic acid (**16b**) (10.9 mg, 0.072 mmol, 2.5 equiv.) in dioxane (0.6 ml) was added K_3PO_4 (10.2 mg, 0.048 mmol, 1.6 equiv.), PPh_3 (5.2 mg, 0.020 mmol, 0.7 equiv.) and $Pd(dba)_2$ (3.0 mg, 5.2 μmol, 0.2 equiv.) successively at room temperature. After stirring for 3 h at 80 °C in an oil bath, the reaction mixture was extracted with AcOEt (X2). The organic layer was washed with brine once and dried over Na_2SO_4. Purification by preparative TLC provided *N*-Ts-amidepyrazine (**17b**) (11.6 mg, 89% yield) as a yellow solid.

Compound **17b**: mp 169.0–169.5 °C. ^{1}H NMR (600 MHz, CDCl3) δ 2.38 (3H, s, Ts), 3.85 (3H, s, OCH_3), 4.24 (2H, s, benzyl), 6.98 (2H, d, *J*=8.4 Hz, anisole), 7.17–7.36 (8H, m, Ar), 7.70 (2H, d, *J*=8.4 Hz, anisole), 7.88 (2H, d, *J*=7.8 Hz, Ts), 8.46 (1H, s, Py) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.0, 40.6, 54.9, 114.9, 127.2, 127.6, 128.8, 129.2, 129.8, 136.0, 136.2, 136.5, 137.2, 143.6, 143.8, 146.8, 160.7 ppm. FAB-MS (NBA) *m/z* 446 (MH^+). HRMS (FAB/NBA) calcd for $C_{25}H_{24}N_3O_3S$ 446.1538, found 446.1515 (MH^+). Anal. calcd for $C_{25}H_{23}N_3O_3S$: C, 67.39; H, 5.20; N, 9.43. Found: C, 67.38; H, 5.17; N, 9.41.

4.1.11. 2-Amino-3-benzyl-5-(4-methoxyphenyl)pyrazine (18b). *N*-Ts-amidepyrazine (**17b**) (25.5 mg, 0.057 mmol) was dissolved in 1.0 ml of conc. H_2SO_4 at 0 °C in an ice bath. After stirring for 20 min at 0 °C, ice was poured into the reaction. The reaction mixture was extracted with CH_2Cl_2 (X3). The organic layer was washed with brine once and then dried over Na_2SO_4. Purification by preparative TLC provided aminopyrazine (**18b**) (8.2 mg, 49% yield) as a yellow solid and *N*-Ts-amidepyrazine (**17b**) (6.6 mg, 26% yield) as recovered starting material.

Compound **18b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s, OCH_3), 4.16 (2H, s, benzyl), 4.32 (2H, s, amine-NH_2), 6.97 (2H, d, *J*=8.8 Hz, anisole), 7.22–7.32 (5H, m, Ph), 7.86 (2H, d, *J*=8.8 Hz, anisole), 8.31 (1H, s, Py) ppm. All the other spectroscopic data were identical with reported data in Ref 10).

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11. Benzylic carbon NMR signals was not observed due the perfect overlapping with the carbon signals of DMSO-d_6.