Synthesis and Characterization of 2-(2-Pyridinyl)pyrazine and 2,2′-Bipyrazine Derivatives

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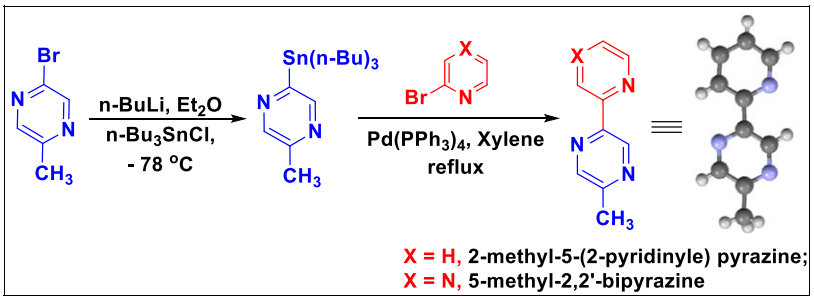

A convenient and high yield preparation of derivatives of 2-(2-pyridinyl)pyrazine and derivatives of 2,2′-bipyrazine compounds from their derivatives of bromopyrazine using Stille coupling is reported. X-ray structures, elemental analyses, ^{1}H, ^{13}C-NMR, and mass spectral data of the compounds are given.

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INTRODUCTION

A central goal of chemical synthesis is to develop efficient and reliable methods for making nitrogen-contained heterocycles. Among nitrogen heterocycles, the derivatives of pyrazine and bipyrazine motives have attracted considerable attention, as it is present in many bacterial studies [1], food, agriculture, medicine [2], and as ligands in coordination chemistry [3].

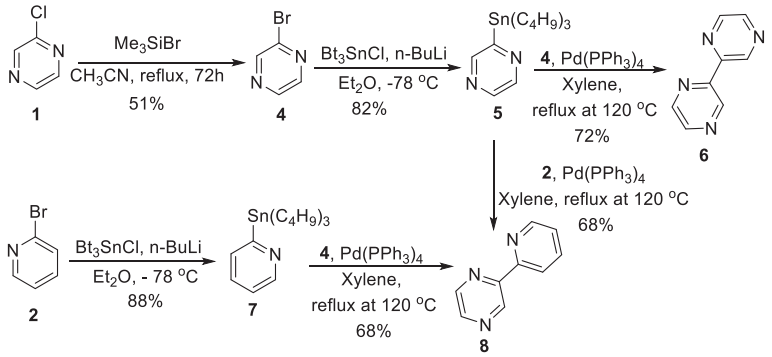
Our group's research efforts have focused on the synthesis and photophysical properties of Re (I) and Ru (II) heterocyclic ligand systems capable of photoexited electron transfer [4–8]. The heterocyclic ligands act as one-electron acceptors upon photoexcitation, and their energetics vary depending upon their aromatic structure, substituents, and whether they are designed as monomers or bridging molecules [4,9–11]. The studies take their impetus from $[Ru(bpy)_3]^{2+}$ (bpy = 2,2′-bipyridine) which has been the most widely studied for several applications [4,12,13]. However, metal complexes with the 2,2′-bipyrazine (bpz) ligand have been used in a variety of systems due to its favorable photophysical properties such as long excited-state lifetimes and high luminescent efficiencies [14–17]. In comparison, the metal-to-ligand charge-transfer band of Ru-bpz complex is slightly higher in energy, and the lifetime of the emissive state is slightly longer than that of Ru-bpy complex in water [17]. Another major difference is their redox potentials, that is, the Ru-bpz potentials are shifted 0.5 V more positive relative to that of Ru-bpy [4]. Because of this importance, the syntheses of derivatives of 2,2′-bipyrazine and 2-(2-pyridinyl)pyrazine compounds are reported in this present work.

The first synthesis of bpz was reported by Lafferty and Case using a copper catalyzed solid-state method [18]. Drawbacks of this protocol were the requirement of high temperatures (270°C) and low yields (7%). Later, Yoon and co-workers described the generation of the bpz ligand by palladium catalysis using conventional methods [3,19,20], and recently, Moeller *et al.* reported its preparation using copper coupling with improved yields [21]. Until now, most of reported protocols were limited to the synthesis of unsubstituted bpz derivatives [22], although in our laboratory, we reported the synthesis and crystal structure of 5,5′-dimethyl-2,2′-bipyrazine (Me_2bpz) [23,24] in very poor yields (<1%). To address the problems associated with previous protocols, we report new synthetic routes for preparing unsubstituted and substituted 2,2′-bipyrazine derivatives using the tributylstannyl pyrazine intermediate (Bu_3SnAr) and Stille coupling [25]. This protocol allows one to synthesize a variety of substituted 2,2′-bipyrazine derivatives and heterobiaryls such as a pyridyl-pyrazine compounds order to expand the study for examining the properties of transition metal complexes.

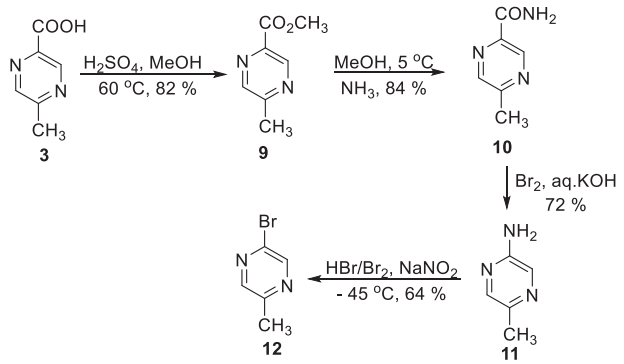
RESULTS AND DISCUSSION

Syntheses. Schemes 1–4 present the syntheses of 2,2′-bipyrazine, its derivatives, and the mixed-ring biaryl *N*-heterocycle containing pyrazine and pyridine, while details of syntheses are given in Experimental Details section. The chemistry of each scheme is summarized in the succeeding texts.

Scheme 1. Synthesis of 2,2′-bipyrazine (**6**) and 2-(2-pyridinyl)pyrazine (**8**).



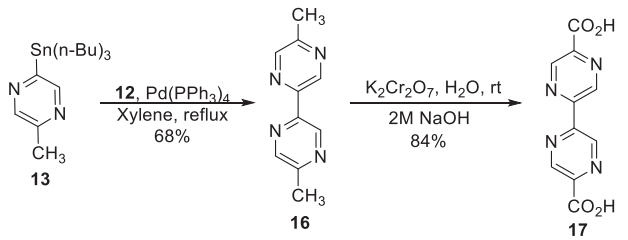
Scheme 2. Synthesis of 2-bromo-5-methylpyrazine (**12**).



The synthesis of 2,2′-bipyrazine started with 2-chloropyrazine (**1**) due to its commercial availability and low cost. It was converted into 2-bromopyrazine (**4**) using the procedure described by Manfred Schlosser *et al*. [26]. The intermediate 2-tributyltinpyarazine (**5**) was prepared by treating 2-bromopyarazine with n-BuLi in ether at −78°C followed by addition of Bu_3SnCl. The Stille coupling reaction with the Pd $(PPh_3)_4$ catalyst was used to synthesize 2,2′-bipyrazine (**6**) [27,28] with an overall yield of 30% yield from **1**.

Two pathways were used to prepare the mixed-ring biaryl *N*-heterocycle containing pyrazine and pyridine (**8**). In one pathway, the intermediate **5** was reacted with 2-bromopyridine to give **8**; in the other pathway, intermediate **7** was reacted with 2-bromopyrazine to give **8** with an overall yield 60%. The overall yield was greater *via* the second route [29].

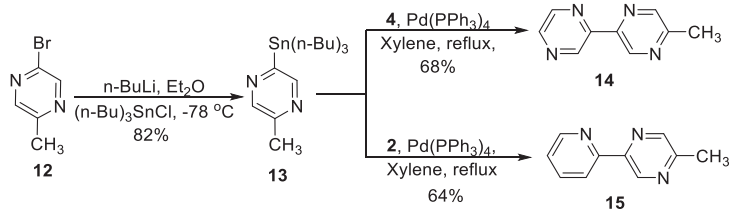
Scheme 4. Synthesis of [2,2′-bipyrazine]-5,5′-dicarboxylic acid (dcbpz) (**17**).



To prepare the 2-bromo-5-methylpyrazine for synthesizing substituted 2,2′-bipyrazine derivatives, the series of reactions shown in Scheme 2 were performed starting with commercially available 5-methylpyrazine-2-carboxylic acid (**3**). Esterification of **3** in the presence of a catalytic amounts of H_2SO_4 provided the intermediate **9** in good yield. Ester **9** was treated with ammonia to generate the amide intermediate **10** which was further converted to 2-amino-5-methylpyrazine **11** using bromine and aq. potassium hydroxide (KOH) by way of the Hoffman rearrangement reaction. Finally, the air sensitive compound, 2-bromo-5-methylpyrazine (**12**), was obtained by reaction with $NaNO_2$, HBr, and Br_2 with an overall yield of 32% from **3** [27,28].

In Scheme 3, 2-bromo-5-methylpyrazine (**12**) was reacted with 2-bromopyrazine to obtain **14** in 56% yield and with 2-bromopyridine to obtain **15** in 53% yield. To the best of our knowledge, it is the first report for the synthesis of the mixed heterocyclic pyrazine-pyridine (**8**) compound.

Scheme 3. Synthesis of 5-methyl-2,2′-bipyrazin (**14**) and 2-methyl-5-(2-pyridinyl)pyrazine (**15**).



The synthesis of [2,2′-bipyrazine]-5,5′-dicarboxylic acid (**17**) is illustrated in Scheme 4. It involves coupling of **13** with **12** and oxidation of the methyl groups with $K_2Cr_2O_7$ to form the carboxyl groups.

The compounds were characterized by elemental analysis, ^1H, ^{13}C-NMR, and mass spectra. Single crystal X-ray structures were obtained for the seven compounds: 2,2′-bipyrazine (**6**), 2-(2-pyridinyl)pyrazine (**8**), methyl-5-methylpyrazine-2-carboxylate (**9**), 5-methylpyrazine-2-carboxamide (**10**), 2-amino-5-methylpyrazine (**11**), 2-bromo-5-methylpyrazine (**12**), and 2-methyl-5-(2-pyridinyl)pyrazine (**15**) [27].

X-ray structure information. Crystal data for **9**, **10**, **11**, and **12** are listed in Table S1, and mercury diagrams are shown in Figure 1. Among these, compounds **11** and **12** are reported in this present work. Compounds **9** and **10** were previously reported by our group [30,31].

Selected bond lengths and bond angles are listed in Table S2. The C-C (Me) bond distance of **9**, **10**, **11**, and **12** are respectively 1.49, 1.49, 1.51, and 1.51 Å, which is within the range of carbon–carbon single bonds. The C=O in **9** is 1.20 Å, and C=O in **10** is 1.24 Å. There is a 0.04 Å variation between **9** and **10**; the C=O bond in **9** is shorter than the C=O bond in **10**. The bond lengths of substituted pyrazines are 1.35 Å for C-NH_2 in compound **11** and 1.89 Å for the C-Br bond in compound **12**.

Crystal data for **6**, **8**, and **15** are listed in Table S3 and mercury diagrams are shown in Figure 2. Compounds **8** and **15** are reported here; compound **6** was reported previously by our group [24]. Selected bond lengths and bond angles are listed in Table S4. The C-C and C-N bonds distances in the pyrazine ring in all compounds are within the range of average values reported previously for related pyrazine and six membered heterocyclic rings [32]. The bond lengths of the C-C bridge are ~1.48 Å whereas those in the six membered rings are ~1.38 Å. The C-N bond lengths in the six membered rings of pyrazine, pyridine, and related six membered heterocyclic substrates are ~1.36 Å [32]. The C-N-C bond angles in the rings are slightly smaller than 120° due to the lone

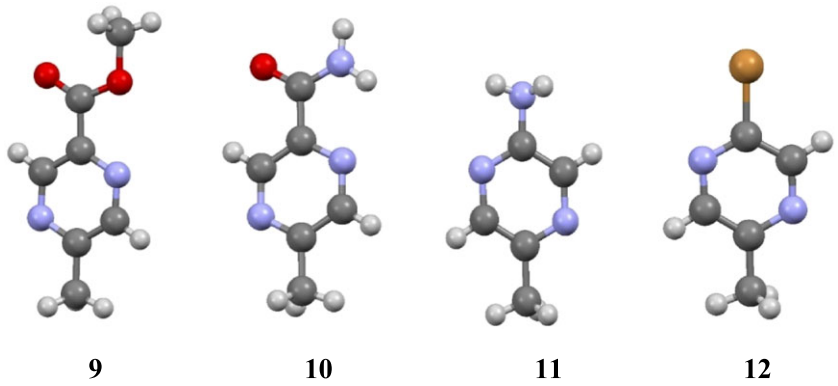


Figure 1. Mercury diagrams are shown for methyl-5-methylpyrazine-2-carboxylate (**9**), 5-methylpyrazine-2-carboxamide (**10**), 2-amino-5-methylpyrazine (**11**), and 2-bromo-5-methylpyrazine (**12**). [Color figure can be viewed at wileyonlinelibrary.com]

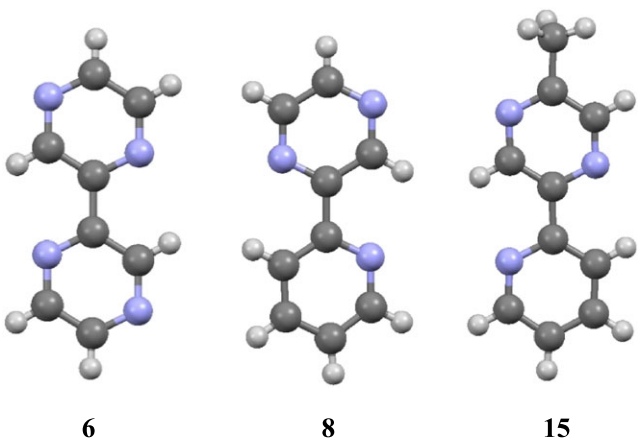


Figure 2. Mercury diagrams are shown for 2,2′-bipyrazine (**6**), 2-(pyridin-2-yl) pyrazine (**8**), and 2-methyl-5-(pyridine-2-yl) pyrazine (**15**). [Color figure can be viewed at wileyonlinelibrary.com]

pair of electron on the N atoms and N-C-C bond angles are larger than 120° which is common in heterocyclic biaryl six-membered rings [33].

CONCLUSIONS

A series of pyrazine compounds leading to their bromo derivatives along with coupling of the bromo species to yield C-C bridged dimers were successfully synthesized and characterized by various analytical techniques. Here, we report the synthesis of 2-(2-pyridinyl)pyrazine derivatives and improved yields of 2,2′-bipyrazine derivatives by using Stille coupling. The performed synthetic route allows one to synthesize a variety of substituted bipyrazine derivatives and heterobiaryls such as 2-(2-pyridinyl)pyrazine in order to use them as ligands for examining the properties of transition metal complexes and for use in the design of biomedical applications.

EXPERIMENTAL DETAILS

Materials. 2-Chloropyrazine (Oakwood Chemicals, 98.0%) **1**, 2-bromopyridine (Sigma Aldrich, 99.8%) **2**, 5-methylpyrazine-2-carboxylic acid **3** (AK Scientific, 99.0%), bromotrimethylsilane (Oakwood Chemicals, 99.0%), tetrakis (triphenylphosphine) palladium (Acros Organics, 9.0%), tri-n-butyltin chloride (Acros Organics, 95.0%), 2.5 M n-butyllithium solution in hexanes (Acros Organics), propionitrile (Acros Organics, 99%), m-xylene (Acros Organics, 99.0%), bromine (Acros Organics, 99.8%), sulfuric acid (Fisher Scientific, 95.0%), diethyl ether (Aldrich, 99.9%), methanol (Fisher Scientific, HPLC grade), chloroform (Fisher Scientific, HPLC grade), methylene chloride (Fisher Scientific, 99%), hexanes (Fisher Scientific, 99%), optima grade tetrahydrofuran (Fisher Scientific, 99.9%), hydrobromic acid (Fisher Scientific, 47–49%), reagent grade sodium chloride, sodium hydroxide, potassium hydroxide, sodium nitrite, anhydrous calcium sulfate, (Fisher Scientific), ammonia gas (Alexander Chemical Corp.), deuterated chloroform (Cambridge Isotope Laboratories, 99.8%), deuterated dimethyl sulfoxide (Cambridge Isotope Laboratories, 99.9%), and tetramethylsilane (Cambridge Isotope Laboratories, 99.9%) were used as received. All coupling reactions were carried out under an inert argon atmosphere.

Characterization. High-resolution ^{1}H and ^{13}C-NMR spectra obtained with INOVA 400 and Mercury 300 MHz spectrometers, respectively, were used to characterize the structures of the synthesized ligands. Samples were dissolved in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6), and tetramethylsilane was used as the internal standard. Elemental analyses were performed by M-W-H Laboratories in Phoenix, AZ. For X-ray crystallographic determinations, crystals were affixed to a nylon cryoloop using oil (Paratone-n, Exxon) and mounted in the cold stream of a Bruker Kappa-Apex-II diffractometer. The temperature of the crystals were maintained at 150 K using a Cryostream 700EX Cooler (Oxford Cryosystems). Signals were measured using a CCD detector at a distance of 50 mm from the crystal with a combination of phi and omega scans. A scan width of 0.5° and scan time of 10 s were employed using graphite monochromated molybdenum Kα radiation (λ = 0.71073 Å) that was collimated to a 0.6-mm diameter. Data collection and reduction were performed using the Bruker Apex2 suite of programs [34]. All available reflections to $2\theta_{max}$ = 52° were harvested and corrected for Lorentz and polarization factors with Bruker SAINT [35]. Reflections were then corrected for absorption, interframe scaling, and other systematic errors with SADABS 2004/1.48 [36]. The structures were solved (direct methods) using SHELX-T [37] and refined (full-matrix least-squares against F^2) with SHELX-L within the OLEX2 software suite [38]. All non-hydrogen atoms were refined using anisotropic thermal parameters. All hydrogen atoms were included at idealized positions; hydrogen atoms were not refined.

Preparation of compounds. ***2-Bromopyrazine (4).*** A mixture of 2-chloropyrazine (20 mL, 22.8 g, 220.00 mmol) **1**, bromotrimethylsilane (52 mL, 30 g, 200.00 mmol), and propionitrile (200 mL) was heated for 3 days (72 h) under reflux [26]. (A white solid formed in the condenser during reflux. It was removed every 10 h with long glass rod). The reaction mixture was then poured into a 2.0 M of aqueous solution of sodium hydroxide (200 mL) followed by adding ice (~100 g). The aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic layers were washed with water (3 × 200 mL) followed by an aqueous saturated NaCl solution (200 mL) and dried with Na_2SO_4. The solvent was removed with a rotary evaporator, and the obtained colorless oil was purified by distillation; BP 60–61°C/10 torr.[21,22]

Color: White, Yield: 51%. d: 1.72 g/mL. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 8.36 (dd, J = 2.8, 1.6 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1.2H), 8.70 (d, J = 1.5 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$,) δ ppm 141.3, 142.8, 144.7, 147.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_4N_2H_3Br$ 157.94; found 157.92, 159.92.

2-(Tributylstannyl)pyrazine (5). 2-Bromopyrazine (3.2 g, 20.12 mmol) and 60 mL of anhydrous diethyl ether were added under a nitrogen atmosphere into a Schlenk flask containing a side-arm stopcock and magnetic stirring bar [14,39]. The flask was cooled to −78°C using dry ice and acetone followed by the dropwise addition of 2.5 M n-BuLi in hexane solution

(10.53 mL, 26.28 mmol). After stirring at −78°C for 2 h, tributyltin chloride (7.12 mL, 23.72 mmol) was added dropwise to the reaction mixture and continued stirring for another 4 h. Then, the cooling bath was removed, and the solution was stirred for an additional 12 h at room temperature. After the solvent was removed under vacuum, 60 mL of anhydrous diethyl ether was added, and then, the mixture was filtered through a sintered glass filter stick to remove solid impurities. Then, the solvent was evaporated under reduced pressure maintaining an inert atmosphere. The resulting portion of 2-(tributylstannyl)pyrazine (6.06 g) was used in the preparation of 2,2′-bipyrazine without any further treatment. Yield: 82%.

2,2′-Bipyrazine (6). 2-(Tributylstannyl)pyrazine (3.06 g, 8.32 mmol) was dissolved in 60 mL of dry xylene in a one neck round-bottom flask under an argon atmosphere [27,40]. Then, the compounds 2-bromopyrazine (1.32 g, 8.32 mmol) and Pd $(PPh_3)_4$ (0.42 g, 0.36 mmol) were added to a three-neck round-bottom flask equipped with a reflux condenser and a magnetic stir bar in a glove bag under argon. The assembly was removed from the glove bag and purged with argon again. Then, the xylene solution containing 2-(tributylstannyl)pyrazine was cannulated into the flask containing 2-bromopyrazine and the palladium catalyst. The reaction mixture was heated under an argon atmosphere at 120°C for 12 h and then cooled to room temperature. The residue was basified with aqueous sodium hydroxide (15 mL, 2 M, pH > 9), and the compound was extracted with toluene and dried over $MgSO_4$. The solvent was removed under rotary evaporation, and then, the crude solid product was purified *via* flash column chromatography (silica gel, 230–450 mesh). First, the impurities were eluted with n-hexane/ethyl acetate (5:1). Then, the desired compound was obtained by eluting with 1:2 n-hexane/ethyl acetate. Finally, the eluting solvent was removed by rotary evaporation to obtain **6** as a light wheat color crystalline powder (0.95 g).

Color: Light Wheat, Yield: 72%. mp, 135–137°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 8.67 (d, J = 1.2 Hz, 2H), 9.60 (d, J = 1.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ ppm 143.5, 143.5, 143.8, 145.2, 145.4, 149.4. HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_8H_6N_4$ 158.05; found 159.00. *Anal*. Calcd for $C_8H_6N_4$: C, 60.75, H, 3.82, N, 35.42. Found. C, 60.12, H, 3.71, N, 35.21.

2-(Tributylstannyl)pyridine (7). The procedure described for the preparation of **5** (see previous texts) was followed using 2-bromopyridine, **2** (2.0 g, 12.65 mmol), 2.5 M n–BuLi (6.10 mL, 15.26 mmol) in hexane, and tributyltin chloride (3.42 mL, 12.65 mmol). The resulting 2-(tributylstannyl)pyridine (3.82 g) was used in the preparation of 2-(2-pyridinyl)pyrazine without any further treatment. Yield: 88%.

2-(2-Pyridinyl)pyrazine (8). The procedure described for the preparation of **6** (see previous texts) was followed using 2-(tributylstannyl)pyridine in place of 2-(tributylstannyl)pyrazine. 2-(Tributylstannyl)pyridine (3.2 g, 8.70 mml) dissolved in 60 mL of xylene was reacted with 2-bromopyrazine (1.38 g, 8.70 mmol) in the presence of Pd $(PPh_3)_4$ (0.36 g, 0.32 mmol). The crude solid product was purified *via* flash column chromatography (silica gel, 230–450 mesh). First, the impurities were eluted with n-hexane/ethyl acetate (6:1). Then, the desired compound was obtained by eluting with 1:2 n-hexane/ethyl acetate. Finally, the eluting solvent was removed by rotary evaporation to obtain **8** as a light wheat color crystalline powder (0.93 g).

Color: Light Wheat, Yield: 68%. mp, 59°C; Anal. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 7.36 (ddd, J = 8.0, 4.8, 1.2 Hz, 1H), 7.84 (td, J = 8.0 Hz, 1.8 Hz, 1H), 8.36 (dt, J = 8.0, 1.2 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.60 (m, 1H), 8.72 (m, 1H), 9.63 (d, J = 1.6 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm: 121.3, 121.6, 124.1, 124.7, 137.0, 143.3, 143.4, 143.8, 144.2, 144.6, 149.3, 151.1, 154.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_7N_3$ 157.00; found 157.92. Calcd for $C_9H_7N_3{\cdot}¼H_2O$: C, 66.86, H, 4.68, 25.99. Found. C, 66.29, H, 4.45, N, 25.39.

Methyl-5-methylpyrazine-2-carboxylate (9). The compounds **9** to **12** were synthesized by minor modification of procedures reported by Madhusudhan *et al*. [29]. 5–Methylpyrazine-2-carboxylic acid **3** (50 g, 0.362 mol) was dissolved in methanol (150 mL) with stirring at 0–5°C. To this solution, 4 mL of concentrated sulfuric acid was added dropwise. Then, the reaction mixture was stirred at 65°C for 8 h. After cooling the solution to room temperature, excess methanol was removed from the solution by rotary evaporation at 30°C. The crude compound was partitioned between water (200 mL) and toluene (300 mL). The water layer was separated from the toluene layer and extracted with toluene (3 × 200 mL). The combined organic layers were washed with 2% aqueous sodium hydroxide solution (50 mL), dried over sodium sulfate, filtered, and concentrated under vacuum at T < 50°C to give the desired compound **9**. The vapor diffusion technique was used to grow crystals. The inner vial contained 5-methyl-2-pyrazinecarboxylate in dichloromethane and the outer vial contained methanol. Crystals were harvested from the inner vial after 36 h.

Color: Light Brown, Yield: 82%. mp, 93°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 2.62 (s, 3H), 3.98 (s, 3H), 8.53 (d, J = 2.0 Hz, 1H), 9.13 (d, J = 2.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ ppm 21.5, 22.1, 52.6, 53.0, 140.3, 143.8, 144.3, 145.0, 145.4, 157, 164.5. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_7H_8N_2O_2$ 153.05; found 153.00. *Anal*. Calcd for $C_7H_8N_2O_2$: C, 55.26, H 5.30, N, 18.41. Found. C, 55.14, H, 5.13, N, 18.64.

5-Methylpyrazine-2-carboxamide (10). Ammonia gas was bubbled into a stirring solution of crude compound **9** (60.0 g, 0.394 mol) in methanol (400 mL) at 0–5°C for 4 h. After completion of the reaction (monitored by TLC), the product was separated by filtration and washed with pre-cooled methanol (2 × 30 mL) to give compound **10**. Crystals were obtained by allowing methanol to evaporate from a solution containing a small amount of compound.

Color: Light Brown, Yield: 84%. mp, 207°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ ppm 2.66 (s, 3H), 5.88 (bs, 2H), 7.59 (bs, 2H), 8.40 (d, J = 2.0 Hz, 1H), 9.28 (d, J = 2.0 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm 141.45, 142.4, 143.4, 143.6, 165.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_6H_7N_3O$ 138.05; found 137.92. *Anal*. Calcd for $C_6H_7N_3O$: C, 52.15, H, 5.14, N, 30.64. Found. C, 53.35, H, 5.23, N, 31.07.

2-Amino-5-methylpyrazine (11). To a stirring solution of potassium hydroxide (72 g, 1.28 mol) in water (400 mL) at 0–5°C, bromine (21 mL, 0.362 mol) was added dropwise at very slow rate. Compound **10** (46 g, 0.336 mol) was then added to the reaction mixture at 5°C. After an hour, another portion of KOH (18 g, 0.302 mol) was added to the reaction mixture at 5°C. Then, the mixture was heated to 85–90°C. After completion of the reaction, (~5 h monitored by TLC), the product was extracted with dichloromethane (3 × 100 mL). The collected organic layers were washed with water, dried with sodium sulfate, and evaporated under reduced pressure to give a residue. The residue was triturated with n-hexane, and the obtained solid was filtered to give compound **11**. Crystals were obtained from the crude product.

Color: Yellow, Yield: 72%. mp, 114–115°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 2.38 (s, 3H), 4.44 (bs, 2H), 7.86 (m, 1H), 7.90 (d, J = 2.0 Hz, 1H); ^{13}C-NMR (300 MHz,$CDCl_3$) δ ppm 19.8, 20.3, 130.8, 131.3, 140.9, 142.5, 152.3. HRMS (ESI) *m/z*: [M+] Calcd for $C_5H_7N_3$ 110.06; found 110.00. *Anal*. Calcd for $C_5H_7N_3$: C, 55.03, H, 6.47, N, 38.50. Found. C, 55.13, H, 6.60, N, 38.61.

2-Bromo-5-methylpyrazine (12). Powdered 2-amino-5-methylpyrazine **11** (6 g, 0.055 mol) was added with vigorous stirring to 48% aqueous hydrobromic acid (100 mL) at a temperature between 25°C to 30°C. (At this point, mechanical stirring replaced magnetic stirring due to the viscous nature of the subsequent reaction.) The reaction mixture was cooled to −50°C by using dry ice–acetone bath after the compound was completely dissolved. Cooled bromine (12 mL) was then added dropwise over 1 h maintaining the temperature at −50°C. Then, sodium nitrite (12 g, 0.173 mol in 24 mL of water) was added dropwise to the reaction mixture while maintaining the temperature at approximately −50°C for 90 min. Then, the reaction mixture was basified with aqueous sodium hydroxide (pH 9) at temperatures below −20°C followed by extraction of the product with n-hexane (3 × 100) which subsequently was concentrated to approximately 50 mL. The concentrate was cooled to −15°C and stirred for 30 min. The white solid that precipitated (**12**) was isolated by filtration. Crystals were obtained by dissolving the compound in hexane solution and placing it in the freezer. Crystals were not stable at room temperature.

Color: White, Yield: 64%. mp, 44–45°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm2.48 (s, 3H), 8.19 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm 20.6, 137.8, 144.3, 146.40, 152.3. HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_5H_5N_2Br$ 172.96; found 172.92, 174.92. *Anal*. Calcd for $C_5H_5N_2Br$: C, 34.71, H, 2.91, N, 16.19. Found. C, 34.17, H, 2.77, N, 16.09.

2-(Tributylstannyl)-5-methylpyrazine (13). The procedure described for the preparation of **5** (see previous texts) was followed using 2-bromo-5-methylpyrazine (3.00 g, 17.34 mmol). It was added to 50 mL of anhydrous diethyl ether under a nitrogen atmosphere into a Schlenk flask containing a side-arm stopcock and magnetic stirring bar. The flask was cooled to −78°C followed by the dropwise addition of 2.5 M n-BuLi in hexane (10.32 mL, 25.8 mmol). After the reaction solution was stirred at −78°C for 2 h (120 min), tributyltin chloride (7.02 mL, 25.8 mmol) was added dropwise to the reaction mixture. Stirring was continued for 4 h. Then, the cooling bath was removed, and the solution was stirred for an additional 12 h at room temperature. The solvent was removed under vacuum. Then, 60 mL of diethyl ether was added. The mixture was filtered to remove solid impurities. Next, the solvent was evaporated under reduced pressure. The resulting 2-(tributylstannyl)-5-methylpyrazine (5.28 g) **13** was used in the preparation of 5,5′-dimethyl-2,2′-bipyrazine without any further treatment. Yield: 82%.

5-Methyl-2,2′-bipyrazine (14). The procedure described for the preparation of **6** (see previous texts) was followed using 2-(tributylstannyl)-5-methylpyrazine in place of 2-(tributylstannyl)pyrazine. 2-(Tributylstannyl)-5-methylpyrazine (3.12 g, 8.16 mml) dissolved in 60 mL of xylene was reacted with 2-bromopyrazine (1.30 g, 8.16 mmol) in the presence of Pd $(PPh_3)_4$ (0.0.40 g, 0.36 mmol). The crude solid product was purified *via* flash column chromatography (silica gel, 230–450 mesh). First, the impurities were removed by eluting with n-hexane/ethyl acetate (3:1). Then, the desired compound was obtained after eluting with n-hexane/ethyl acetate (1:3). Finally, the eluting solvent was removed by rotary evaporation to obtain **14** as a white color crystalline powder (1.04 g).

Color: White, Yield: 68%. mp, 183°C, ^{1}H-NMR ($CDCl_3$, 400 MHz): δ ppm 2.65 (s, 3H), 8.67 (s, 2H), 8.51 (s, 1H), 9.41 (d, J = 2.0 Hz, 1H), 9.60 (d,

J = 1.2 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm 21.9, 142.2, 142.4, 143.1, 143.3, 143.5, 143.5, 143.9, 144.6, 145.0, 146.4, 149.6, 154.7. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_8N_4$ 172.07; found 173.00. *Anal*. Calcd for $C_9H_8N_4$: C, 62.78, H, 4.68, N, 32.54. Found. C, 62.60, H, 4.46, N, 32.41.

2-Methyl-5-(2-pyridinyl)pyrazine (15). A modification of the procedure described for the preparation of **6** (see previous texts) was followed. 2-(Tributylstannyl)-5-methylpyrazine (3.12 g, 8.16 mmol) in 60 mL of xylene was reacted with 2-bromopyridine (1.28 g, 8.16 mmol) in the presence of Pd $(PPh_3)_4$ (0.40 g, 0.36 mmol). The crude solid product was purified *via* flash column chromatography (silica gel, 230–450 mesh). First, the impurities were removed by eluting with n-hexane/ethyl acetate (3:1). Then, the desired compound was obtained after eluting with n-hexane/ethyl acetate (1:3). Finally, the eluting solvent was removed by rotary evaporation to obtain **15** as a white color crystalline powder (0.93 g).

Color: White, Yield: 64%. mp, 73°C ^{1}H-NMR ($CDCl_3$, 400 MHz): δ ppm 2.66 (s, 3H), 8.22 (d, J = 7.6 Hz, 1H), 7.71 (dd, J = 1.8, 1.2 Hz, 1H), 8.22 (d, J = 1.8 Hz, 1H), 8.38 (dd, J = 2.4, 1.2 Hz, 1H), 8.60 (dd, J = 2.4, 1.6 Hz, 1H), 9.41 (dd, J = 2.4, 1.2 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm 21.3, 120.9, 123.9, 136.8, 142.0, 143.1, 148.1, 143.9, 153.5. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_9N_3$ 171.07; found 172.00.; *Anal*. Calcd for $C_{10}H_9N_3$: C, 70.16, H, 5.30, N, 24.54. Found. C, 70.49, H, 5.36, N, 24.71.

5,5′-Dimethyl-2,2′-bipyrazine (16). A modification of the procedure described for the preparation of **6** (see previous texts) was followed. 2-(Tributylstannyl)-5-methylpyrazine (1.75 g, 4.73 mmol) in 40 mL of xylene was reacted with 2-bromo-5-methylpyrazine (0.78 g, 4.56 mmol) in the presence of Pd $(PPh_3)_4$ (0.24 g, 0.21 mmol). The solid was removed under rotary evaporation, and then, the crude solid product was purified *via* flash column chromatography (silica gel, 230–450 mesh) using n-hexane/ethyl acetate (5:1) as eluent. Final, the eluting solvent was removed by rotary evaporator to obtain **16** as a white color crystalline powder (0.58 g).

Color: White, Yield: 68%. mp, 148°C, *Anal*. ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 2.65 (s, 6H), 8.51 (d, J = 2.0 Hz, 2H), 9.41 (d, J = 1.2 Hz, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ ppm 21.52, 142.0, 143.4, 146.7, 154.1.17. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}N_4$ 186.09; 187.00. Calcd for $C_{10}H_{10}N_4$: C, 64.50, H, 5.41, N, 30.09. Found. C, 64.76, H 5.49, N, 30.00.

[2,2′-Bipyrazine]-5,5′-dicarboxylic acid (17). Potassium dichromate (3.4 g, 3.8 mmol) was added in small portions to a stirring solution of 5,5′-dimethyl-2,2′-bipyrazine (0.72 g, 3.88 mmol) in sulfuric acid (60 mL, 98%) initially at 70°C. (Occasional cooling with a water bath during the addition of potassium dichromate was necessary to maintain the temperature between 70°C and 80°C). Heating was discontinued after all the potassium dichromate was added. The resulting deep green mixture was poured into 500 mL of ice water. After the temperature fell below 40°C, a light-green colored precipitate was collected, washed with water until the filtrate was white, and allowed to dry. The resulting white solid was further purified by refluxing it in 60 mL of 50% nitric acid for 4 h. This solution was poured over ice in 1 L of water. The solid **17** was removed by filtration, washed with water (40–50 mL) and then with acetone, (3 × 15 mL) and allowed to dry.

Color: White, Yield: 84%. ^{1}H-NMR (400 MHz, DMSO): δ ppm 9.34 (d, J = 1.2 Hz, 2H), 9.65 (d, J = 2.4 Hz, 2H); ^{13}C-NMR (300 MHz, DMSO) δ ppm 139.2, 145.4, 158.9, 162.2, 180.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_6N_4O_4$ 246.03; found 247.00. *Anal*. Calcd for $C_{10}H_6N_4O_4 \cdot 1½H_2O$: C, 43.92, H, 3.29, N, 20.50. Found. C, 44.29, H, 3.80, N, 20.30.

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