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Chemical Transformation of Pyrazine Derivatives

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Abstract

Pyrazine is a group of *N*-containing heterocycle compounds found in both nature and synthetic drugs. In fact, the existence of the pyrazine ring as a basic framework in many drug compounds indicates that these compounds are important in drug development/design. Pyrazine as medicinal compounds, especially as anticancer, contain amine or amide groups, while some functional groups, like bromo, methyl, methoxy, nitro, amino, and methylamino have antimigration and antiproliferative activities. Based on these considerations, various chemical transformations, consisting of nitration, acetylation, esterification, bromination, and amidation have been carried out on commercially available pyrazine based starting materials containing amine or amide groups. Those chemical transformation resulting in seven pyrazine derivatives that have the potential to be applied as anticancer, namely 3-hydroxy-6-nitropyrazine-2-carboxamide **(1)**, 3-(acetylcarbamoyl)-5-bromopyrazine-2-yl acetate **(2)**, methyl 3-aminopyrazine-2-carboxylate **(3)**, 3-amino-*N*-phenylpyrazine-2-carboxamide **(4)**, 3-amino-*N*-methylpyrazine-2-carboxamide **(5)**, methyl 3-amino-6-bromopyrazine-2-carboxylate **(6)**, and 3,5-dibromopyrazine-2-amine **(7)**. The molecular structures of these compounds were elucidated based on the ^{1}H NMR, ^{13}C NMR and Mass Spectral data.

Keywords: *Pyrazine; Drugs Development; Chemical Transformation; Molecular Structure*

1. Introduction

Pyrazine is a heterocyclic aromatic compound with two nitrogen atoms at positions 1 and 4, known as *p*-diazin or 1,4-diazin [1]. Pyrazine is abundant in nature, especially as alkyl pyrazine, with the main function as a flavoring agent as a result of spontaneously induced condensation between amino acids and sugars through Strecker degradation [2, 3]. Although many pyrazines are found in nature, the content of pyrazine in natural product is very small. Meanwhile, the demand for pyrazine in the industrial world is increasing and cannot only be met by isolation from natural products because of the low yield, so pyrazine synthesis is necessary. Synthesized pyrazine derivatives are not only used industrially for flavoring agent, but also in the pharmaceutical industry. Several pyrazine derivatives are commonly used as diabetic drugs, namely glipizide (A) [4,5], amiloride (B) [6], and benzamyl (C) [7]. In addition, pyrazine derivatives are also used as anticancer agents, including bortezamine (D) [8], and zibotentan (E) [9]. Other pyrazine derivatives, morinamide (F) [10] and pyrazinamide (G) [11] are used as antitubercular. Favipiravir (H) and telepavir (I) are derivatives of pyrazine compounds that are used as antiviral drugs. Favipiravir is currently widely used as a drug for coronavirus disease which appeared in 2019 caused by the SARS-Cov-2 virus [12]. Meanwhile, telepavir is used as a hepatitis drug because this compound inhibits the protease activity of the hepatitis C virus and HIV [13]. The existence of the pyrazine ring as the basic framework in various clinically used drugs indicates that this compound is important in drug development/design, but to obtain optimal bioactivity of pyrazine compounds, various modifications of the molecular structure are required. The bioactivity of a compound is related to the molecular structure. The structure of pyrazines that act as drug compounds has a similarity (Figure 1.), which contains the amine group (Amiloride, Benzamyl, Zibotentan) and amides group (glipizide, bortezomib, morinamida, pyrazinamide, favipiravir, and telepavir). Thus, pyrazine derivatives with amine and amide groups have the potential to be developed as medicinal compounds such as diabetic drugs, anticancer, antitubercular and antivirus. Meanwhile, in previous studies it was mentioned that several functional groups, such as bromo, methyl, methoxy, nitro, amino, and methylamino have antimigration and antiproliferative activities, which are related to anticancer [14]. Based on this background, in this study, various chemical transformations (nitration, acetylation, esterification, bromination, and amidation) of the pyrazine containing amine or amide groups were carried out to obtain various pyrazine derivatives that have the potential to be applied as medicinal compounds, especially as anticancer.

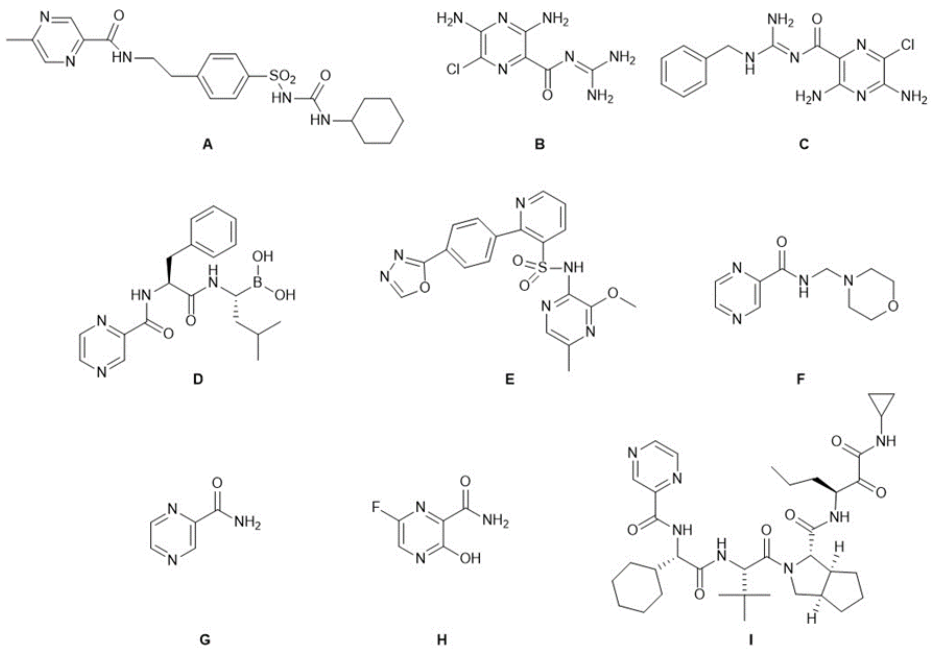


Figure 1. Pyrazine-based drug compounds

2. Experimental

2.1. Materials

Chemicals used in the synthesis were reagents grade or with a higher purity level purchased from Merck, Sigma-Aldrich including 3-hydroxypyrazine-2-carboxamide **(a)**, 6-bromo-3-hydroxypyrazine-2-carboxamide **(b)**, and 3-aminopyrazine-2-carboxylic acid **(c)**, potassium nitrate, sulfuric acid, acetic acid anhydride, methanol, thionyl chloride, 1,1'-carbonyldiimidazole (CDI), aniline, dimethyl sulfoxide (DMSO), methylamine, triethylamine, bromine, and trichloromethane. The solvent used for chromatography is a technical grade that has been distilled beforehand. TLC was performed out on an aluminum plate coated with silica gel Merck Kieselgel 60 F254 0.25 mm. Determination of molecular structure using Agilent V NMR (^{1}H 500 MHz and ^{13}C 125 MHz) at 25 ^{0}C, and Waters LCT Premier XE ESI-TOF (Electron Spray Ionization-Time of Flight).

2.2. Methods

2.2.1. Synthesis of 3-hydroxy-6-nitropyrazine-2-carboxamide (1)

1.0 gram (7 mmol, 1 eq) of **a** was dissolved in 6 mL of concentrated sulfuric acid at an ice bath temperature (under ice-cooling) and stirred with a magnetic stirrer. Potassium nitrate was added to the mixture as much as 1.4 g (14 mmol, 2 eq), then stirred at 50 ^{0}C for 4 hours. The mixture was put into 60 mL of distilled water at an ice bath temperature (under ice-cooling). The precipitate formed was filtered through a buchner filter and dried. The product was obtained without further purification in the form of a yellowish-white solid as much as 1.025 g (79.6%). ^{1}H NMR (DMSO-d_6): 8.96 (*s*, 1H), 8.31 (*s*, 1H), 8.06 (*s*, 1H). ^{13}C NMR (DMSO-d_6): 163.2, 156.4, 142.9, 138.2, 133.7. TOF MS (ESI): $[M+H]^+$ ion *m/z* 185.0301 (calc. $[M+H]^+$ ion for $C_5H_5N_4O_4^+$: *m/z* 185.031).

2.2.2. Synthesis of 3-(acetylcarbamoyl)-5-bromopyrazine-2-yl acetate (2)

250 mg (1,15 mmol, 1 eq) of **b** was added with 5 mL of acetic anhydride and stirred at 100 ^{0}C overnight while monitored by TLC. The solution was allowed to stand at room temperature until precipitated, then filtered and dried. The product obtained in the form of brown solids as much as 255 mg (73.5%). ^{1}H NMR ($CDCl_3$): 8.74 (*s*, 1H), 9.92 (*bs*, 1H), 2.57 (*s*, 3H), 2.47 (*s*, 3H). ^{13}C NMR ($CDCl_3$): 171.5, 168.3, 166.4, 153.5, 150.3, 135.6, 135.2. TOF MS (ESI): $[2M+Na]^+$ ion *m/z* 626.9478 (calc. $[2M+Na]^+$ ion for $C_{18}H_{16}Br_2N_6O_8Na^+$: *m/z* 626.9480).

2.2.3. Synthesis of methyl 3-aminopyrazine-2-carboxylate (3)

417 mg (3 mmol, 1 eq) of **c** was dissolved in 25 mL of methanol then added with 0.655 mL (9 mmol, 3 eq) of $SOCl_2$ dropwise in an ice bath. The mixture was stirred at 75 ^{0}C for 4 hours. The solution was poured into 10 mL of water then evaporated under vacuum to remove $SOCl_2$. The concentrated solution was neutralized with $NaHCO_3$ saturated solution (pH=7) and extracted with 3 x 10 mL DCM. The DCM phase was dried with anhydrous Na_2SO_4 then filtered and concentrated under vacuum. The product obtained in the form of yellow solid as much as 306 mg (66.7 %). ^{1}H NMR ($CDCl_3$): 8.22 (*d*, 1H, *J*=2.35), 8.01 (*d*, 1H, *J*=2.35), 6.43 (*bs*, 2H), 4.00 (*s*, 3H). ^{13}C NMR ($CDCl_3$): 166.8, 155.9, 147.6, 133.6, 124.3, 53.8. TOF MS (ESI): $[M+H]^+$ ion *m/z* 154.06617 (calc. $[M+H]^+$ ion for $C_6H_8N_3O_2^+$: *m/z* 154.0617).

2.2.4. Synthesis of 3-amino-N-phenylpyrazine-2-carboxamide (4)

100 mg (0.72 mmol, 1 eq) of **c** was dissolved in 1.5 mL of DMSO and added with 152 mg of 1,1'-carbonyldiimidazole (CDI), stirred at room temperature for approximately 10 minutes. The solution was added with 200 µL (2.1 mmol, 3 eq) of aniline and stirred again at 100 ^{0}C for 3 hours. The aliquot was monitored by TLC using n-hexane: ethyl acetate

= 2:1 as the eluent. The solution is poured into 6 mL of water and then filtered. The solid formed was dissolved with acetone, dried with anhydrous Na_2SO_4 then evaporated under vacuum. The product was gray solid as much as 79.6 mg (53.2 %). ^{1}H NMR ($CDCl_3$): 9.81 (*bs*, 1H), 8.21 (*d*, 1H, *J*=2.35), 7.87 (*d*, 1H, *J=3.35*), 7.71 (*dd*, 2H, *J*=1.35, *J*=8.65), 7.30-7.37 (*m*, 2H), 7.17-7.15 (*m*, 1H). ^{13}C NMR ($CDCl_3$): 163.9, 155.4, 147.1, 137.4, 131.5, 126.2, 124.4, 129.1, 119.8. TOF MS (ESI): $[M+H]^+$ ion *m/z* 215.0922 (calc. $[M+H]^+$ ion for $C_{11}H_{11}N_4O^+$: *m/z* 215.0933).

2.2.5. Synthesis of 3-amino-N-methylpyrazine-2-carboxamide (5)

100 mg (0.65 mmol, 1 eq) of **3** was added with 4 mL of methanol then stirred at 100 ^{0}C. After complete dissolution, added 180 µL (1.95 mmol, 6 eq) of methylamine and 190 µL (1.3 mmol, 2 eq) of triethylamine in the solution, stirred again at 100 ^{0}C for 5 hours. The aliquot was monitored by TLC using n-hexane: ethyl acetate = 1:1 as eluent, then the solution was concentrated under vacuum and then purified using a chromatotron with n-hexane: ethyl acetate = 4: 1 as eluent. The product was obtained in the form of white solid as much as 27.4 mg (27.8%). ^{1}H NMR ($CDCl_3$): 8.13 (*d*, 1H, *J*=2.45), 7.89 (*bs*, 1H), 7.76 (*d*, 1H, *J*=2.45), 2.98 (*d*, 3H, *J*=5.05). ^{13}C NMR ($CDCl_3$): 166.6, 155.9, 146.5, 131.5, 126.7, 25.9. TOF MS (ESI): $[M+H]^+$ ion *m/z* 153.0772 (calc. $[M+H]^+$ ion for $C_6H_9N_4O^+$: *m/z* 153.0776).

2.2.6. Synthesis of methyl 3-amino-6-bromopyrazine-2-carboxylate (6) and 3,5-dibromopyrazine-2-amine (7)

50 mg (0.325 mmol, 1 eq) of **3** was added with 6 mL of trichloromethane, then 0.5 mL of Br_2 was added dropwise. The mixture was stirred for 20 minutes at room temperature and monitored by TLC, then concentrated under vacuum and purified by chromatotron using n-hexane: ethyl acetate = 4: 1 as eluent. The product was obtained in the form of brown solids of methyl 3-amino-6-bromopyrazine-2-carboxylate **(6)** as much as 24.6 mg (34%) and brown pale solid 3-amino-6-bromopyrazine-2-carbonyl bromide **(7)** as much as 8 mg (8.8%). **(6)** ^{1}H NMR ($CDCl_3$): 5.09 (*s*, 2H), 8.29 (*s*, 1H), 3.98 (*s*, 3H). ^{13}C NMR ($CDCl_3$): 166.0, 154.7, 150.2, 143.1, 124.8, 53.0. TOF MS (ESI): $[M+H]^+$ ion *m/z* 231.9712 (calc. $[M+H]^+$ ion for $C_6H_7N_3O_2Br^+$: *m/z* 231.9722). **(7)** ^{1}H NMR ($CDCl_3$): 5.07 (*bs*, 2H), 8.29 (*s*, 1H). ^{13}C NMR ($CDCl_3$): 151.8, 150.2, 143.1, 123.9. TOF MS (ESI): $[M+H]^+$ ion *m/z* 251.8762 (calc. $[M+H]^+$ ion for $C_4H_4N_3Br_2^+$: *m/z* 251.8772).

3. Results and discussion

Various chemical transformations have been carried out on the available pyrazine starting materials to produce seven pyrazine derivatives. In this study, three available pyrazine starting materials were used, **a**, **b** and **c**. Nitration of **a** produces **1**, whereas acetylation of **b** produces **2**. For **c**, several steps of chemical transformation have been carried out, esterification of **c** produced **3**, meanwhile, the one-step reaction between **c** and aniline using CDI produced **4**. The reaction of **3** with methylamine produced **5**. The reaction of **3** with bromine produced **6** and **7 (Figure 2.)**. The molecular structures of these compounds were elucidated based on the ^{1}H NMR and ^{13}C NMR spectra and TOF MS (ESI) spectra.

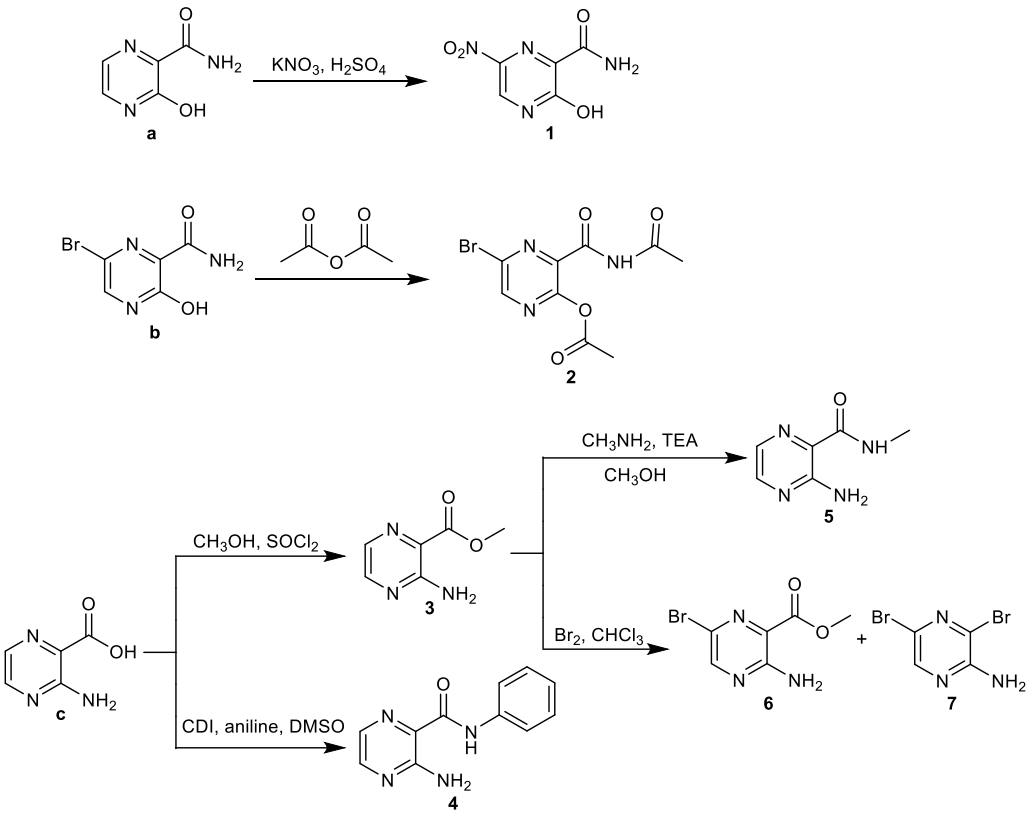


Figure 2. Chemical transformation of pyrazine

3.1. 3-hydroxy-6-nitropyrazine-2-carboxamide (1)

1 is the nitration product of **a**, prepared by reacting one equivalent of **a** with two equivalents of KNO_3 using an H_2SO_4 catalyst. Apart from being a catalyst, H_2SO_4 also functions as a solvent. Starting material **(a)** has the characteristic of being difficult to dissolve in organic solvents. In acidic H_2SO_4, **a** which is basic can dissolve completely. The position of the nitro group is influenced by the amide group as a *m*-director and the hydroxyl group as an *o,p*-director, where the two groups reinforce each other so that nitro substitution occurs at position 6. The resulting product is a pale-yellow solid with a yield of 79.6%. These results are much better than previously reported studies [15]. The molecular structure of **1** was determined based on the ^1H and ^{13}C NMR and MS spectra. The ^1H NMR spectrum showed the appearance of three hydrogen peaks. The peak at δ_H 8.96 was a signal from the proton of the pyrazine (C5) while the peaks at δ_H 8.06 and 8.31 were respectively the signals of two protons of the amide group ($CONH_2$), while the proton signal of the OH group was not visible. From the ^{13}C NMR spectrum, five carbon peaks with appropriate chemical shifts for 3-hydroxy-6-nitropyrazine-2-carboxamide **(1) (Table 1.)** were obtained. The results of TOF MS (ESI) analysis showed that there were two peaks with values of *m/z*:185.0301 $[M+H]^+$ and *m/z*: 207.0122 $[M+Na]^+$, while the *m/z* $[M+H]^+$ calc. for $C_5H_5N_4O_4^+$: 185.0311. These results are suitable for **1** with the molecular formula $C_5H_4N_4O_4$. The results of these measurements show agreement with the literature [15] in the ^1H NMR, ^{13}C NMR, and TOF MS (ESI) spectra.

3.2. 3-(acetylcarbamoyl)-5-bromopyrazine-2-yl acetate (2)

2 is the acetylation product of 6-bromo-3-hydroxypyrazine-2-carboxamide **b**, prepared by reacting **b** with an excess acetic acid anhydride. This reaction is mild because it is catalyst-free and solvent-free [16], under the perspective of green chemistry, and can provide high yields. The use of excess acetic acid anhydride allows acetylation to occur twice (diacetylation). The oxygen atom has more lone pairs of electrons than the nitrogen atom, so that the first

acetylation occurs through hydrogen substitution of the free hydroxyl group to produce 5-bromo-3-carbamoylpyrazine-2-yl acetate, and the second acetylation occurs through hydrogen substitution of the amide group to give **2 (Figure 3.)**. The lone pair electron in oxygen and nitrogen attacks the carbonyl group in acetic anhydride to produce the corresponding ester by releasing acetic acid. Furthermore, the liberated acetic acid protonates the carbonyl group of acetic anhydride and undergoes a series of steps so that the hydrogen atom can be replaced by an acetyl group [16].

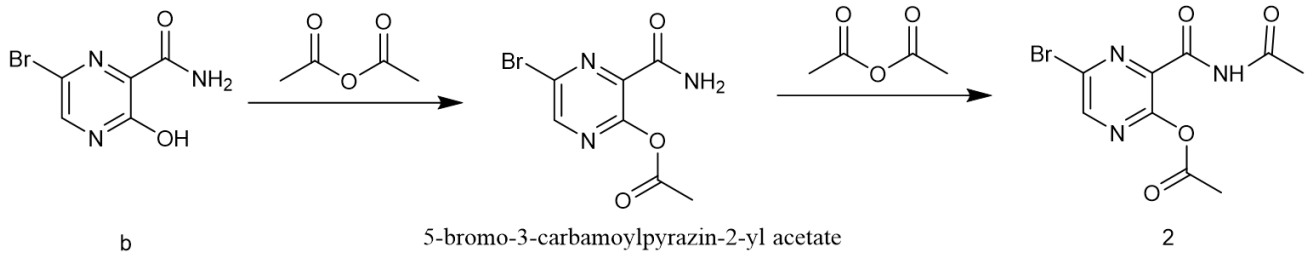


Figure 3. Diacetylation of 5-bromo-3-hydroxypyrazine-2-carboxamide **(b)**

Confirmation of the molecular structure of **2** was shown from the ^{1}H NMR spectrum by a singlet peak at δ_H 9.92 which was the amide hydrogen, and two signals at δ_H 2.57 ppm and 2.47 ppm, respectively, indicating the existence of two acetyl groups. Meanwhile, from the ^{13}C NMR spectrum, the existence of two acetyl groups was indicated by two singlet peaks at δ_C 171.5 ppm and 168.3 ppm. The measured proton and carbon signals indicated suitability for compound **2 (Table 1.)**. The result of TOF MS (ESI) analysis showed a peak with *m/z*: 626.9478 $[2M+Na]^+$ while the *m/z* $[2M+Na]^+$ calc. for $C_{18}H_{16}Br_2N_6O_8Na^+$: 626.9480. These results are suitable for **2** with the molecular formula $C_9H_8BrN_3O_4$.

3.3. methyl 3-aminopyrazine-2-carboxylate (3)

3 is the acetylation product of **c**, prepared by reacting one equivalent of **c** with three equivalents of $SOCl_2$ and excess methanol [17]. The addition of $SOCl_2$ was carried out in an ice bath temperature because the reaction was exothermic and to reduce excess smoke from $SOCl_2$. The reaction was carried out at 75 ^{0}C for 4 hours. The work-up process is carried out by adding the solution to water, because it dissolves well in water [18], then evaporated with a rotary evaporator to remove residual $SOCl_2$ and methanol. Extraction with DCM was carried out to remove water.

The esterification was developed in two steps, the first is the reaction between **c** and $SOCl_2$ to produce 3-aminopyrazine-2-carbonyl chloride. At this step there is a change from the OH to Cl which is a better leaving group. Furthermore, 3-aminopyrazine-2-carbonyl chloride reacts with methanol to produce **3 (Figure 4.)**. The product was obtained in the form of a yellow solid with a yield of 66.7%.

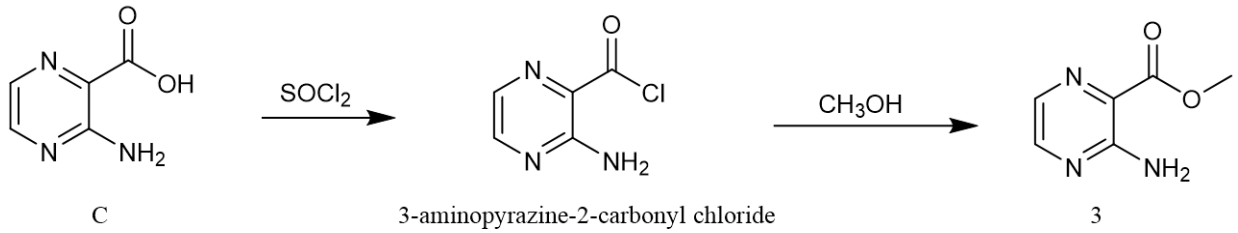


Figure 4. Formation of methyl 3-aminopyrazine-2-carboxylate **(3)**

The molecular structure of **3** was elucidated by ^{1}H NMR spectrum due to the appearance of a signal at δ_H 4.00 as a singlet relative to methoxy hydrogens. The two hydrogen pyrazines at C5 and C6 appear as doublets at δ_H 8.22 and 8.01, respectively, while the two amine hydrogens appear as a singlet at δ_H 6.43 ppm. Confirmation of the molecular structure of **3** was also obtained from the ^{13}C NMR spectrum due to the appearance of a signal at δ_C 52.9 relative to methoxy carbon (Table 1). The measurement of carbon NMR for **3** show agreement with the literature [19]. The result of TOF MS (ESI) analysis showed a peak with *m/z*:154.0617 $[M+H]^+$ while the *m/z* $[M+H]^+$ calc. for $C_6H_8N_3O_2^+$: 154.0617. These results are suitable for **3** with the molecular formula $C_6H_7N_3O_2$.

3.4. 3-amino-N-phenylpyrazine-2-carboxamide (4)

4 is the amidation product of 3-aminopyrazine-2-carboxylic acid **c**, prepared by reacting one equivalent of **c** with three equivalents of aniline using 1,2 equivalents of CDI in DMSO as the coupling agent [20]. CDI serves to activate carboxylic acids, changing the hydroxyl group of the acid from an unfavorable leaving group to a good leaving group, before being reacted with amines [21]. The reaction between **c** and CDI forms the intermediate (3-aminopyrazine-2-yl)(1H-imidazole-1-yl)methanone, which then reacts with aniline to form **4 (Figure 5.)**. Workup is done by pouring the solution into the water followed by extraction with DCM to remove DMSO. **4** is not soluble in water, so when poured into water, **4** will form as a precipitate and can be separated. The product obtained is a gray solid with a yield of 53.2%.

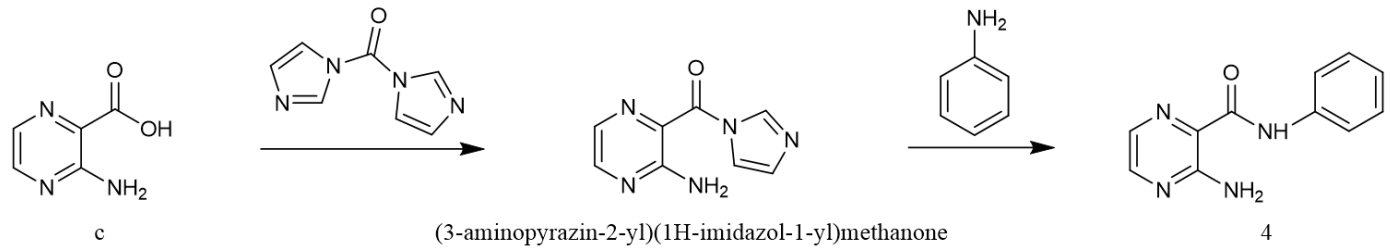


Figure 5. Formation of 3-amino-N-phenylpyrazine-2-carboxamide **(4)**

The molecular structure of **4** was confirmed due to the appearance of a signal at δ_H 9.81 as a singlet relative to amide hydrogen which binds to the carbonyl group and aromatic ring. Meanwhile, the existence of aromatic rings was shown by typical signals at δ_H 7.71, 7.30-7.37, and 7.17-7.15 and δ_C 119.8, 124.4, 129.1 and 137.4 **(Table 1)**. The results obtained from these measurements also show an agreement with the literature [20]. The result of TOF MS (ESI) analysis showed a peak with *m/z*:215.0922 $[M+H]^+$ while the *m/z* $[M+H]^+$ calc. for $C_{11}H_{11}N_4O^+$: 215.0933. These results are suitable for **4** with the molecular formula $C_{11}H_{10}N_4O$.

3.5. 3-amino-N-methylpyrazine-2-carboxamide (5)

5 is the amidation product of **3** which developed in two steps reaction. The first step is esterification of **c** to **3**. This step is the activation of carboxylic acids, which is changing the hydroxyl group into methoxyl which is a good leaving group. The second stage is the formation of amides, which is reacting **3** (1eq) with methylamine (6 eq) to form **5 (Figure. 6)**. In this second stage, TEA (2 eq) is used as a base catalyst [22] and methanol as a solvent [20]. The molecular structure of **5** was determined by the appearance of δ_H 7.89 as a broad singlet indicating the existence of amide hydrogen and δ_H 2.98 as a doublet (J = 5.05 Hz) indicating the existence of methyl hydrogen. The two doublet peaks at 8.13 ppm and 7.76 ppm represent hydrogen signals at the C5 and C6 pyrazine rings, respectively. From the ^{13}C NMR spectrum, six carbon signals with chemical shifts corresponding to **5** were obtained **(Table 1)**. The peak at

25.9 ppm as the carbon signal from N-methyl confirms the structure of **5**. Proton and carbon NMR chemical shift of **5** correspond to 3-amino-*N*-penthylpyrazine-2-carboxamide [20] where the two compounds differ only in the alkyl chain. The result of TOF MS (ESI) analysis showed a peak with *m/z*:153.0772 $[M+H]^+$ while the *m/z* $[M+H]^+$ calc. for $C_6H_9N_4O^+$: 153.0776. These results are suitable for **5** with the molecular formula $C_6H_8N_4O$.

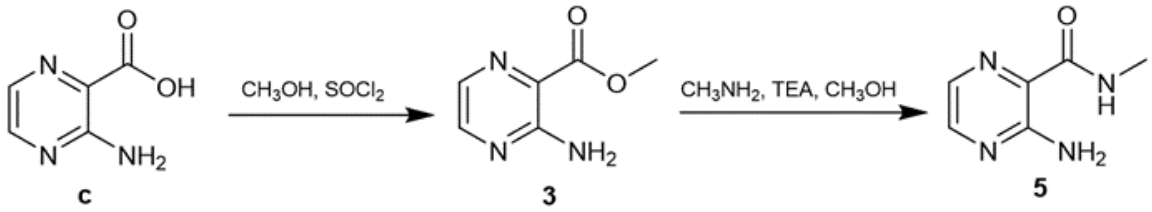


Figure 6. Formation of 3-amino-*N*-methylpyrazine-2-carboxamide **(5)**

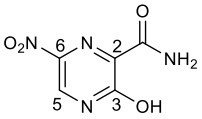
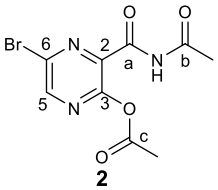
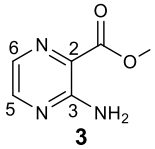
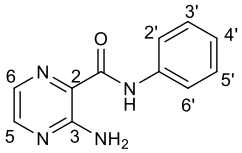
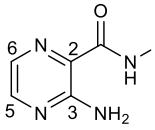
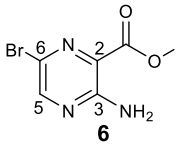
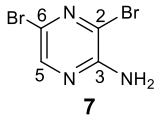
3.6. methyl 3-amino-6-bromopyrazine-2-carboxylate (6) and 3,5-dibromopyrazine-2-amine (7)

6 and **7** are brominated products of **3** using an excess bromine in chloroform. Br_2 performs electrophilic substitution on the heterocyclic aromatic ring. The substitution occurs at position 6 due to the directing effect of the mutually reinforcing amine (o,p) and carboxylate (m) groups. The product resulting from this substitution is **6**. With an excess of reagent, the 1st eq of Br_2 performs an electrophilic substitution on the heterocyclic aromatic ring at position 6 to give **6**, and the 2nd eq of Br_2 give **7**. Confirmation of the molecular structure of **6** was obtained from the appearance of δ_H 3.98 as a singlet and δ_C 53.0 which indicated the presence of a methoxyl group while in compound **7** the two peaks were not found **(Table 1)**. Proton and carbon NMR chemical shift of **6** correspond to 3-amino-6-bromo-*N*-methylpyrazine-2-carboxamide [23] where the two compounds differ only in the methoxy and *N*-methyl group. The result of TOF MS (ESI) analysis showed a peak with *m/z*:231.9712 $[M+H]^+$ while the *m/z* $[M+H]^+$ calc. for $C_6H_7N_3O_2Br^+$: 231.9722. The result is suitable for **6** with the molecular formula $C_6H_6N_3O_2Br$. Compared with the NMR spectra of the substrate **(3)**, the hydrogen signal at position 6 is no longer present both on **6** and **7**, because it was substituted by Bromine. In **7**, the peak indicating the existence of carbonyl and methoxy group which was originally present in **3** and **6** was not found, both in the ^1H NMR and ^{13}C NMR spectra. This indicates that in **7**, the carbonyl and the methoxy group has also been substituted by bromide. The presence of 2 Br in **7** can be proven by the results of the TOF MS (ESI) measurement wich showed a peak at *m/z*: 251.8762 $[M+H]^+$ while the *m/z* $[M+H]^+$ calc. for $C_4H_4N_3Br_2^+$: 251.8772. The result is suitable for **7** with the molecular formula $C_4H_3N_3Br_2$.

4. Conclusion

Various chemical transformation has been made to the available pyrazine starting materials resulting in seven pyrazine derivatives, namely 3-hydroxy-6-nitropyrazine-2-carboxamide **(1)**, 3-(acetylcarbamoyl)-5-bromopyrazine-2-yl acetate **(2)**, methyl 3-aminopyrazine-2-carboxylate **(3)**, 3-amino-*N*-phenylpyrazine-2-carboxamide **(4)**, 3-amino-*N*-methylpyrazine-2-carboxamide **(5)**, methyl 3-amino-6-bromopyrazine-2-carboxylate **(6)**, and 3,5-dibromopyrazine-2-amine **(7)**.

Table 1. The proton and carbon chemical shift of pyrazine derivatives

Pyrazine derivative	C/H	δ_H (*mult.*, *J* in Hz)	δ_C	Refference	
				δ_H (*mult.*, *J* in Hz)	δ_C
 **1**	C2	-	142.9	-	142.5
	C3-OH	-	163.2	12.00-15.00 (*br s*)	163.1
	C5-H	8.96 (*s*)	138.2	8,97 (*s*)	138.2
	C6-NO_2	-	133.7	-	133.8
	$CONH_2$	8.06 (*s*)	156.4	8.06 (*s*)	156.5
		8.31 (*s*)		8.32 (*s*)	
					[15]
 **2**	C2	-	150.3		
	C3-O-	-	153.5		
	C5-H	8.74 (*s*)	135.6		
	C6-Br	-	135.2		
	-$CO_{(a)}$-NH-	9.92 (*bs*)	166.4		
	-$CO_{(b)}$-CH_3	2.57 (*s*)	171.5		
	-$CO_{(c)}$-CH_3	2.47 (*s*)	168.3		
 **3**	C2	-	124.3	-	124.5
	C3-NH_2	6.43 (*bs*)	155.9	-	156.2
	C5-H	8.22 (*d*, 2.35)	147.6	-	147.8
	C6-H	8.01 (*d*, 2.35)	133.6	-	133.8
	COO-	-	166.8	-	167.1
	-OCH_3	4.00 (*s*)	52.9	-	52.9
					[19]
 **4**	C2	-	126.2	-	126.2
	C3-NH_2	-	155.4	-	155.3
	C5-H	8.21 (*d*, 2.35)	147.1	8.20 (*d*, 2.4)	147.0
	C6-H	7.87 (*d*, 2.35)	131.5	7.86 (*d*, 2.3)	131.5
	CO-NH-	9,81 (*bs*)	163.9	9.81 (*s*)	163.9
	C1’	-	137.4	-	137.4
	C2’/C6’	7.71 (*dd*, 1.35, 8.65)	119.8	7.73-7.68 (*m*)	119.8
	C3’/C5’	7.30-7.37 (*m*)	129.1	7.42-7.36 (*m*)	129.0
	C4’	7.17-7.15 (*m*)	124.4	7.19-7.14 (*m*)	124.4
					[20]
 **5**	C2	-	126.7	-	126.7
	C3-NH_2	-	155.9	-	155.0
	C5-H	8.13 (*d*, 2.45)	146.5	8.13 (*d*, 2.4)	146.3
	C6-H	7.76 (*d*, 2,45)	131.5	7.77 (*d*, 2.3)	131.4
	CONH-	7.89 (*bs*)	166.6	7.91	165.8
	-CH_3	2.98 (*d*, 5.05)	25.9	-	-
					[20]
 **6**	C2	-	150.2		
	C3-NH_2	5.09 (*s*)	154.7		
	C5-H	8.29 (*s*)	143.1		
	C6-Br	-	124.8		
	COO-	-	166.0		
	-OCH_3	3.98 (*s*)	53.0		
 **7**	C2-Br	-	150.2		
	C3-NH_2	5.09 (*bs*)	151.8		
	C5-H	8.29 (*s*)	143.1		
	C6-Br	-	123.9		

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