A General and Efficient Route to 6-Methyl-pyrazin-2-yl-amines: Alkylation of 2,6-Dichloropyrazine *via* Malonate Derivatives

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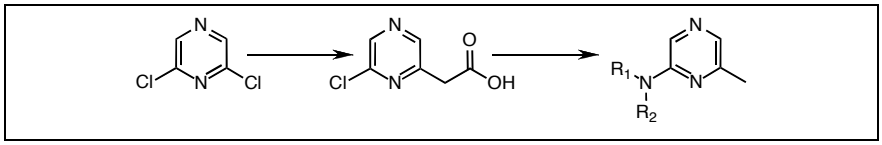

We have developed a convenient two-stage process for the synthesis of 6-methylpyrazine-2-yl-amines from commercially available materials. The procedure involves the synthesis of (6-chloro-pyrazin-2-yl)-acetic acid *via* arylation of diethyl malonate and *in situ* hydrolysis/decarboxylation. A second decarboxylation takes place under the subsequent amination conditions allowing simple and efficient access to the intended pyrazines.

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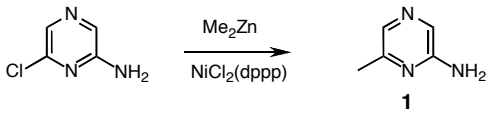
INTRODUCTION

We recently required a convenient synthesis of 6-methyl-pyrazin-2-yl-amine **1**, which was an important intermediate in the synthesis of several compounds within our drug development program. A number of routes to **1** have been described in the literature but none are particularly efficient or amenable to large-scale manufacture [1-3]. For example, a one-step procedure starting from readily available 2-amino-6-chloropyrazine had been employed within our Medicinal Chemistry function, based on a nickel-catalysed Negishi coupling with dimethylzinc (Scheme 1) [3].

Scheme 1

Route to **1** *via* Negishi coupling.

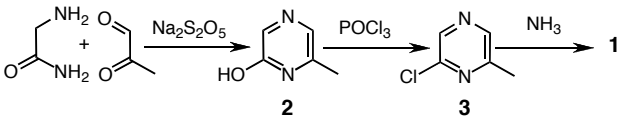


This procedure could be used to produce multi-gram quantities of **1** in 50 % yield after chromatographic purification, and the conditions could be modified to widen the scope significantly as reported recently [3]. The main drawback with this process is the need for an excess of the hazardous (pyrophoric) dimethylzinc reagent, which would present significant challenges to scale up in the longer term. To produce the early hundred-gram quantities of **1** a reported synthetic route which formed the pyrazine ring from glycinamide and pyruvic aldehyde was used with an overall yield of 12 % (Scheme 2) [1].

Unfortunately, the capricious nature of the pyrazine ring formation, the difficult isolations of 2-hydroxy-6-methylpyrazine **2** and the low-melting, volatile intermediate 2-chloro-6-methylpyrazine **3** made this synthesis, in our view, unsuitable for multi-kilo scale manufacture. We therefore sought alternative methodology for introduction of the methyl group into the pyrazine nucleus.

Scheme 2

Initial drug discovery route to **1**.

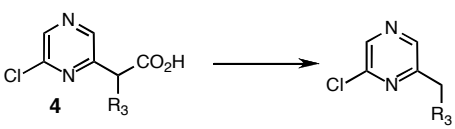


RESULTS AND DISCUSSION

There are a number of reports of displacement of halogens from halopyrazines and halobenzopyrazines with a variety of stabilized carbanions [4]. However we were aware of only anecdotal reports of decarboxylation of pyrazinyl acetic acids **4** derived from 2,6-dichloropyrazine leading to alkyl substituted pyrazine products (Scheme 3) [5,6]. Of particular note is the adventitious decarboxylation of a molecule of type **4** (R_3 = alkyl) upon treatment with triethylamine in ethyl acetate at reflux, surprisingly mild conditions that presumably owe their success to the electron-withdrawing nature of the pyrazine ring (Scheme 3) [5].

Scheme 3

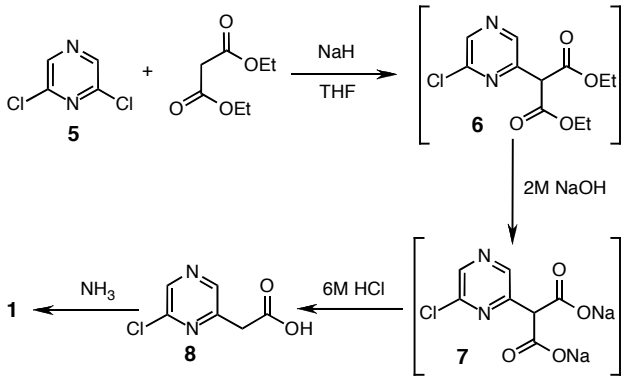
Decarboxylations of Pyrazin-2-yl-acetic acid.



These reports suggested to us that a novel alternative route to **1** from commercially available 2,6-dichloropyrazine **5** might be feasible, *via* initial chloride displacement with a malonate anion to produce 2-(6-chloropyrazin-2-yl)-malonic acid diethyl ester **6** (Scheme 4). The second chloride displacement with ammonia and a double decarboxylation would then complete the synthesis. In practice we discovered that the sodium salt of 2-(6-chloro-pyrazin-2-yl)-malonic acid **7** undergoes a facile initial decarboxylation to give the highly crystalline (6-chloro-pyrazin-2-yl)-acetic acid **8** which is next subjected both to the second decarboxylation and amination in the same step. Whilst **5** is quite expensive on a small-scale, large-scale supply costs are relatively low and this two stage route in which **8** is the only isolated intermediate had potential for further development and scale-up as described below.

Scheme 4

Drug development route to **1**.



Crude 2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **6** was prepared by reaction of the sodium salt of diethyl malonate (two equivalents) with **5** at reflux. The excess sodium hydride and diethyl malonate were required due to the relatively acidic proton of **6**. A lower conversion of **5** to product was achieved if two equivalents of sodium hydride were used with only one equivalent of diethyl malonate. Following an acid quench, the organic layer was partially concentrated *in vacuo* (to remove THF) and to give a solution of **6** and the excess diethyl malonate. Isolation of **6** was investigated, but even after purification by chromatography the compound remained an oil. Separating **6** from the excess diethyl malonate in future was likely to require vacuum distillation or chromatography, which would be both expensive and time consuming on a multi-kilo scale. Therefore, effort focused on developing hydrolysis conditions using the mixture of diethyl malonate and **6**.

Both acidic and basic conditions for the ester hydrolysis were examined. Of the acidic conditions investigated, the use of sulfuric acid in acetic acid (60 °C, 24 h) appeared most efficient. However, minimizing the second decarboxylation reaction, which produced **3**, proved difficult. Increasing the temperature and duration of the reaction to achieve complete formation of **3** was possible, but extensive decomposition was observed, and this compound had already been deemed an undesirable intermediate due to its poor physical properties.

The ester hydrolysis under basic conditions was achieved at 20 °C, and at this lower temperature the reaction was much more selective than any of the acidic hydrolysis conditions screened. No evidence of double decarboxylation was observed and under these conditions minor non-acidic impurities were also removed *via* a methyl isobutyl ketone wash prior to the acidification. The use of sodium hydroxide solution (2 *M*) provided the optimum balance of reaction rate, volume efficiency and solubility for the hydrolysis reaction. The result was an aqueous layer containing **7**, which was added slowly to hydrochloric acid (6 *M*), initiating the first decarboxylation. The order of addition and the reaction temperature (20-25 °C) were crucial to maintaining an addition-rate controlled reaction and hence a controlled evolution of carbon dioxide. The resulting acid **8** partially precipitated from the mixture, but in order to maximize yield and for ease of isolation, the product was extracted into methyl isobutyl ketone and concentrated *in vacuo*. The resulting crude solid was then purified by crystallization from methyl *tert*-butyl ether.

In the final step, amination by displacement of chloride as well as the second decarboxylation were achieved, by treatment of **8** with aqueous ammonia in a sealed vessel at 180 °C. Water was added at the end of reaction, and the ammonia removed by evaporation *in vacuo* to facilitate an efficient extraction of the product into ethyl acetate. A charcoal treatment of the organic layer, before concentration *in vacuo* gave **1** as a pale orange solid in good yield and >99% purity by GC. The compound was subsequently used in our drug discovery program as an intermediate without any further purification.

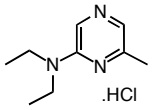
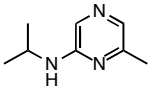
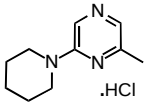
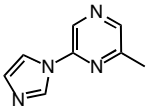
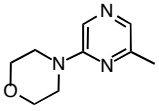
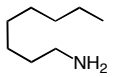
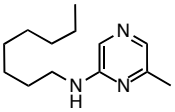
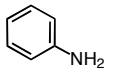
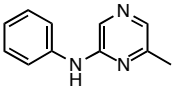
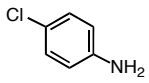
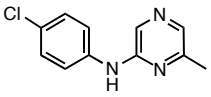
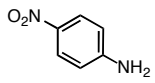
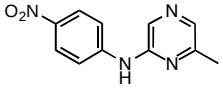
In order to broaden the utility of our new process we sought to synthesize a variety of 6-methyl-pyrazin-2-yl-amines. To explore the scope and limitations of the nucleophilic aromatic substitution of **8** with a range of amines, a set of standard reaction conditions was required. The aqueous amination conditions used in the synthesis of **1** were not suitable for many potential hydrophobic amines. A short reaction screen was conducted to establish a suitable set of conditions that promoted amination. Initially five solvents of varying polarity, both protic and aprotic, were chosen (*N*-methylpyrrolidinone, sulfolane, isoamyl alcohol, diglyme and xylene) and two amines (benzylamine and *p*-nitroaniline) were examined. The high boiling solvents allowed reactions to be carried out in conventional glassware, this coupled with the use

of aromatic amines facilitated reaction monitoring (by HPLC) over different reaction times and temperatures. The two amines chosen offered a range of nucleophilicity which was designed to allow further differentiation of the solvents performance, should similar conversions be obtained in different solvents using an amine considered to be a good nucleophile. The output from this screen indicated that *N*-methylpyrrolidinone (10 vol.), 6 equivalents of amine and a reaction temperature of 160 °C for 20 hours was likely to ensure good conversion. The excess amine could be recycled or lower equivalents could be used successfully if the amine was valuable but this would prolong reaction times.

In order to investigate the effect of both steric and electronic properties for this nucleophilic aromatic substitution and synthesize a range of potentially useful pyrazines **9** - **17**, nine amines were chosen. The range included primary, secondary, aliphatic, cyclic and aromatic amines (Table 1).

Table 1

Amination of (6-chloro-pyrazin-2-yl)-acetic acid **8**.

Entry	Amine	Product	Yield (%)
1		**9** 	53
2		**10** 	61
3		**11** 	77
4		**12** 	75
5		**13** 	82
6		**14** 	87
7		**15** 	82
8		**16** 	39
9		**17** 	0

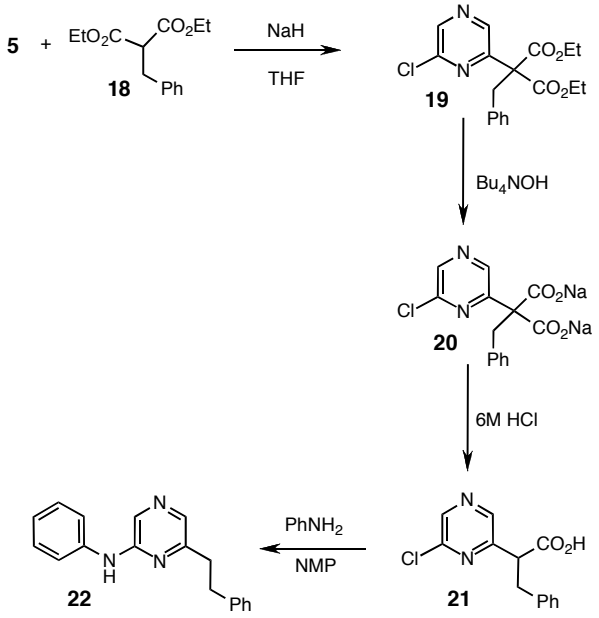
For each reaction, **8** was dissolved in *N*-methylpyrrolidinone, 6 equivalents of the amine added and the solution heated at 160 °C for 20 hours. Amines that had a boiling point lower than 160 °C were investigated under the same optimized conditions but in a sealed vessel. The isolated yields obtained for these reactions showed good correlation with the nuleophilicity of the starting amine. Excellent yields have been obtained for good nucleophiles such as benzylamine and octylamine, whist the substituted aniline examples clearly indicate the effect on the yield of reducing anilines nucleophilicity with electron withdrawing groups.

A control experiment in which **8** was simply heated in *N*-methylpyrrolidinone at 150 °C showed that the decarboxylation is relatively fast, complete conversion to **3** being observed within 2 hours. Thus, the process proceeds *via* initial formation of **3** *in situ,* followed by a slower nucleophilic substitution of the chloride by the amines.

Finally we have shown that a substituted malonate, 2-benzyl-malonic acid diethyl ester **18** will also react with **5**. The resulting product was then hydrolysed, decarboxylated and aminated using aniline, to demonstrate the potential for further expansion of the range of aminopyrazines that can be synthesized (Scheme 5).

Scheme 5

Synthesis of a 2,6-pyrazine *via* substituted malonate **18**.



2-Benzyl-malonic acid diethyl ester **18** was used to generate the corresponding 2-benzyl-2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **19**, which could be isolated as a crystalline solid. The subsequent hydrolysis required the addition of tetrabutylammonium hydroxide

as **19** appeared completely insoluble when subjected to our standard sodium hydroxide (2 *M*), hydrolysis conditions. The resulting intermediate **20** was again decarboxylated without isolation to furnish 2-(6-chloro-pyrazin-2-yl)-3-phenyl-propionic acid **21**, whilst the subsequent amination with aniline was carried out using our standard conditions to produce the desired (6-phenethyl-pyrazin-2-yl)-phenyl-amine **22**. Although no optimisation of this route was carried out this demonstrates the potential scope for expansion beyond methylpyrazine, *via* the use of other malonates or carbanions.

In conclusion, we have demonstrated a new synthetic route to 6-methyl-pyrazin-2-yl amines, in two stages *via* an easily isolated intermediate from relatively cheap and available starting materials. The new route has been used to produce **1** on multigram scale giving an overall yield of 48 % and should be more amenable for further development into a multi-kilo process than any currently reported route [1-3]. The process is also suitable for a range of amines giving access to a potentially useful variety of 6-methyl-pyrazine-2-yl-amines. Finally the use of a substituted malonate indicates the potential scope to develop the syntheses of other 2,6-substituted pyrazines, which may subsequently be investigated.

EXPERIMENTAL

2-(6-Chloro-pyrazin-2-yl)-malonic acid diethyl ester 6. To a suspension of sodium hydride [60 % dispersion in mineral oil] (11.2 g, 279.1 mmol) in tetrahydrofuran (THF) (60 mL) at 0 °C was added diethyl malonate (42.4 mL, 279.1 mmol) in THF (60 mL) followed by a solution of 2,6-dichloropyrazine **5** (20.0 g, 132.9 mmol) in THF (40 mL). The mixture was then heated to reflux for 18 h before being allowed to cool and 2 *M* hydrochloric acid (100 mL) added. The resulting two layers were separated and the organic layer partially concentrated under vacuum (removing the THF) to give a solution containing 2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **6** and diethyl malonate.

The crude 2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **6** can be purified by chromatography on silica eluting with dichloromethane/isohexane (4/1) providing the compound as a clear colourless oil. ^{1}H NMR (400 MHz, dimethyl sulfoxide d_6) δ 8.82 (1H, s), 8.76 (1H, s), 5.39 (1H, s), 4.20 (2 x 2H, q, J = 10.2 Hz), 1.20 (2 x 3H, t, J = 10.2 Hz). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 166.1, 148.9, 147.2, 143.8, 143.7, 61.8, 56.5, 13.7. ESI MS (*m/z*) 273/275 (M+H). HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_{14}N_2O_4Cl$: 273.0642, found: 273.0635. *Anal*. Calcd. for $C_{11}H_{13}ClN_2O_4$: C, 48.45; H, 4.81; N, 10.27. Found: C, 48.40; H, 5.10; N, 9.97.

6-Chloro-pyrazin-2-yl-acetic acid 8. The crude solution of 2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **6** (131 mmol) containing approximately one equivalent of diethyl malonate was cooled to 10 °C and 2 *M* aqueous sodium hydroxide (328 mL) added. After stirring for 24 h the mixture was washed with methyl isobutyl ketone (200 mL) and the organic layer discarded. The aqueous layer containing 2-(6-chloro-pyrazin-2-yl)-malonic acid, sodium salt **7** was then added to 6 *M* hydrochloric acid (135 mL), maintaining a reaction temperature of 20-25 °C to facilitate the decarboxylation. The resulting 6-chloro-pyrazin-2-yl-acetic acid **8**, was extracted into methyl isobutyl ketone (130 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow solid. The resulting crude solid 22.4 g was then crystallised from methyl *tert*-butyl ether to give 6-chloro-pyrazin-2-yl-acetic acid **8** as a white solid, 15.4 g, 89.2 mmol (67 % yield based on 2,6-dichloropyrazine). Melting point: 120-121 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6): δ 12.77 (1H, s), 8.71 (1H, s), 8.67 (1H, s), 3.88 (2H, s). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 170.7, 151.2, 147.3, 143.8, 142.4, 40.0. ESI MS (*m/z*) 173/175 (M+H). HRMS (ESI): $[M+H]^+$ calcd. for $C_6H_6N_2O_2Cl$: 173.0115, found: 173.0118. *Anal*. Calcd. for $C_6H_5ClN_2O_2$: C, 41.76; H, 2.92; N, 16.23. Found: C, 41.56; H, 2.97; N, 16.10.

6-Methyl-pyrazin-2-ylamine 1. To 6-chloro-pyrazin-2-yl-acetic acid **8** (20.0 g, 115.9 mmol) was added 35 % aqueous ammonia (120 mL) and the mixture was then placed in a sealed vessel at 180 °C for 8 h (35 bar pressure observed). The mixture was cooled to 20 °C and water (40 mL) was added before being concentrated under vacuum to remove the ammonia. Water (40 mL) was then added to the residue before the product was extracted into ethyl acetate (2 x 80 mL). The solution was treated with charcoal (3 g) and stirred for 5 minutes before being filtered. The resulting solution was then dried using magnesium sulfate, filtered and evaporated to give 6-methyl-pyrazin-2-ylamine **1** as a pale orange solid 9.0 g, 82.5 mmol (71 % yield based on 6-chloro-pyrazin-2-yl-acetic acid). Melting point: 124-125 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6): δ 7.68 (1H, s), 7.57 (1H, s), 6.27 (2H, br s), 2.21 (3H, s). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 155.2, 150.3, 130.6, 129.1, 20.7. HRMS (ESI): $[M+H]^+$ calcd. for $C_5H_8N_3$: 110.0715, found: 110.0718. *Anal*. Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.50. Found: C, 54.91; H, 6.46; N, 38.17.

Optimised procedure for the synthesis of 6-methyl-pyrazin-2-yl amines 9-17. The reagent amine (6 equiv) was added to a solution of **8** (1.0 g, 5.8 mmol) in *N*-methyl-pyrrolidinone (10 mL) and heated to 160 °C for 20 h. The reaction mixture was purified by ion exchange column chromatography using a Varian SCX column and an eluent of methanol, followed by ammonia in methanol solution. The product containing eluent was concentrated *in vacuo* and further purified by chromatography on silica (particle size: 60A) (eluent: either dichloromethane/methanol or ethyl acetate/isohexane) to give the desired 6-methyl-pyrazin-2-yl amine. When the product existed as an oil, it was converted into its hydrochloride salt by addition of hydrochloric acid in methanol, and the solid salt isolated by filtration.

Diethyl-(6-methyl-pyrazin-2-yl)-amine hydrochloride 9. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with dichloromethane/methanol (400/1) to give the product oil, which was converted to its hydrochloride salt, a yellow solid, 0.6 g, 3.1 mmol, yield 53 %. Melting point: 139-140 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 8.04 (1H, s), 7.74 (1H, s), 3.56 (4H, q, J = 7.0 Hz), 2.40 (3H, s), 1.13 (6H, t, J = 7.0 Hz). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 153.3, 152.8, 124.2, 122.5, 41.8, 21.4, 12.4. HRMS (ESI): $[M+H]^+$ calcd. for $C_9H_{16}N_3$: 166.1344, found: 166.1340. *Anal*. Calcd. for $C_9H_{16}N_3Cl$: C, 53.59; H, 8.00; N, 20.83. Found: C, 53.72; H, 7.94; N, 21.00.

Isopropyl-(6-methyl-pyrazin-2-yl)-amine 10. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with dichloromethane/methanol (200/1) to give the product as a brown solid, 0.6 g, 3.8 mmol, yield 64 %. Melting point: 72-73 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 7.66 (1H, s), 7.49 (1H, s), 6.75 (1H, d, J = 6.9 Hz), 4.0-3.9 (1H, m), 2.23 (3H, s), 1.14 (6H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 153.7, 150.0, 129.9, 129.4, 41.1, 22.3, 21.1. HRMS (ESI): $[M+H]^+$ calcd. for $C_8H_{14}N_3$: 152.1188, found: 152.1168. *Anal*. Calcd. for $C_8H_{13}N_3$: C, 63.55; H, 8.67; N, 27.79. Found: C, 63.61; H, 8.61; N, 27.72.

2-Methyl-6-piperidin-1-yl-pyrazine hydrochloride 11. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with dichloromethane/methanol (400/1) to give the product oil, which was converted to its hydrochloride salt, a yellow solid, 1.0 g, 4.5 mmol, yield 77 %. Melting point: 162-163 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 8.25 (1H, s), 7.77 (1H, s), 3.7-3.6 (4H, m), 2.40 (3H, s), 1.7-1.5 (6H, m). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 154.1, 153.2, 124.5, 123.3, 45.0, 24.9, 23.9, 21.3. HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_{16}N_3$: 178.1344, found: 178.1356. *Anal*. Calcd. for $C_{10}N_{16}N_3Cl$: C, 56.20; H, 7.55; N, 19.66. Found: C, 56.29; H, 7.51; N, 19.89.

2-Imidazol-1-yl-6-methyl pyrazine 12. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with dichloromethane/methanol (39/1) to give the product as a brown solid, 0.7 g, 4.5 mmol, yield 75 %. Melting point: 93-94 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 9.01 (1H, s), 8.59 (1H, s), 8.54 (1H, s), 8.0-7.9 (1H, m), 7.2-7.1 (1H, m), 2.57 (3H, s). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 152.4, 144.1, 142.3, 135.1, 132.0, 130.4, 116.4, 20.9. HRMS (ESI): $[M+H]^+$ calcd. for $C_8H_9N_4$: 161.0827, found: 161.0821. *Anal*. Calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.97; H, 4.91; N, 34.91.

4-(6-Methyl-pyrazin-2-yl)-morpholine 13. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with ethyl acetate/isohexane (1/3) to give the product as a pale orange solid, 0.9 g, 4.8 mmol, yield 82 %. Melting point: 65-66 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 8.10 (1H, s), 7.77 (1H, s), 3.7-3.6 (4H, m), 3.5-3.4 (4H, m), 2.31 (3H, s). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 154.0, 150.0, 132.1, 127.9, 65.8, 44.3, 21.0. HRMS (ESI): $[M+H]^+$ calcd. for: $C_9H_{14}N_3O$: 180.1137, found: 180.1138. *Anal*. Calcd. for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.19; H, 7.26; N, 23.41.

(6-Methyl-pyrazin-2-yl)-octylamine 14. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with ethyl acetate/isohexane (3/17) to give the product as an orange solid, 1.1 g, 5.1 mmol, yield 87 %. Melting point: 34-35 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 7.68 (1H, s), 7.50 (1H, s), 6.85 (1H, t, J = 5.4 Hz), 3.3-3.2 (2H, m), 2.24 (3H, s), 1.5-1.4 (2H, m), 1.3-1.2 (10H, m), 0.9-0.8 (3H, m). ^{13}C NMR (100 MHz, dimethyl sulfoxide d_6) δ 154.4, 149.9, 129.6, 129.5, 40.0, 31.2, 28.7, 28.7, 28.6, 26.5, 22.0, 21.0, 13.9. HRMS (ESI): $[M+H]^+$ calcd. for $C_{13}H_{24}N_3$: 222.1970, found: 222.1981. *Anal*. Calcd. for $C_{13}H_{23}N_3$: C, 70.54; H, 10.47; N, 18.98. Found: C, 70.75; H, 10.60; N, 18.69.

(6-Methyl-pyrazin-2-yl)-phenylamine 15. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with ethyl acetate/isohexane (1/3) to give the product as a brown solid, 0.9 g, 4.8 mmol, yield 82 %. Melting point: 115-116 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 9.36 (1H, s), 8.04 (1H, s), 7.81 (1H, s), 7.7-7.6 (2H, m), 7.3-7.2 (2H, m), 7.0-6.9 (1H, m), 2.36 (3H, s). ^{13}C NMR (75 MHz, dimethyl sulfoxide-d_6) δ 151.5, 149.7, 140.8, 132.5, 131.5, 128.7, 121.1, 118.1, 21.0. HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_{12}N_3$: 186.1031, found: 186.1013. *Anal*. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.07; H, 5.97; N, 22.46.

(4-Chloro-phenyl)-(6-methyl-pyrazin-2-yl)-amine 16. The title compound was obtained according to the general procedure; the crude product was purified by chromatography on silica eluting with dichloromethane/methanol (100/1) and treatment with charcoal to give the product as a white solid, 0.5 g, 2.3 mmol, yield 39 %. Melting point: 132-133 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 9.52 (1H, s), 8.03 (1H, s), 7.85 (1H, s), 7.8-7.7 (2H, m), 7.4-7.3 (2H, m), 2.37 (3H, s). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 151.1, 149.7, 139.8, 132.9, 131.6, 128.5, 124.4, 119.5, 21.0. HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_{11}N_3Cl$: 220.0642, found: 220.0638. . *Anal*. Calcd. for $C_{11}H_{10}N_3Cl$: C, 60.14; H, 4.59; N, 19.13. Found: C, 60.01; H, 4.57; N, 19.02.

2-Benzyl-2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester 19. To a suspension of sodium hydride [60 % dispersion in mineral oil] (1.0 g, 24.2 mmol) in THF (15 mL) at 0 °C was added 2-benzyl-malonic acid diethyl ester **18** (5.2 mL, 22.2 mmol) in THF (12 mL) followed by a solution of 2,6-dichloropyrazine **5** (3.0 g, 20.1 mmol) in THF (6 mL). The mixture was then heated to reflux for 18 h before being allowed to cool to 25 °C and 2 *M* hydrochloric acid (15 mL) was added. The resulting two layers were separated and the aqueous layer was washed with methyl *tert*-butyl ether (30 mL). The combined organic layers were washed with brine (15 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil. The compound was then purified by flash chromatography on silica (particle size: 60 Å) eluting with dichloromethane/isohexane (1/1) providing the compound as a waxy solid, which was then crystallised from isohexane to give the compound as a white solid 4.5 g, 12.4 mmol, yield 62 %. Melting point: 61-62 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6) δ 8.46 (1H, s), 8.29 (1H, s), 7.2-7.1 (3H, m), 6.9-6.8 (2H, m) 4.3-4.2 (2 x 2H, m), 3.70 (2H, s), 1.2-1.1 (2 x 3H, m). ^{13}C NMR (100 MHz, dimethyl sulfoxide-d_6) δ 167.5, 151.4, 146.5, 143.8, 143.0, 134.6, 130.0, 128.2, 127.3, 64.7, 62.0, 40.7, 13.6. HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{20}N_2O_4Cl$: 363.1112, found: 363.1099. *Anal*. Calcd. for $C_{18}H_{19}N_2O_4Cl$: C, 59.59; H, 5.28; N, 7.72. Found: C, 59.71; H, 5.28; N, 7.70.

2-(6-Chloro-pyrazin-2-yl)-3-phenyl-propionic acid 21. To a solution of 2-benzyl-2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester **19** (4.0 g, 11.0 mmol) in THF (4 mL) was added 2 *M* aqueous sodium hydroxide (16.5 mL, 33.1 mmol) followed by tetra-*n*-butylammonium hydroxide (10.5 mL, 16.2 mmol). After stirring for 24 h the mixture was diluted with water (22.5 mL) and washed with methyl *tert*-butyl ether (22.5 mL) and the organic layer discarded. The aqueous layer containing 2-benzyl-2-(6-chloro-pyrazin-2-yl)-malonic acid, sodium salt **20** was then added to 6 *M* hydrochloric acid (10.5 mL), maintaining a reaction temperature of 20-25 °C to facilitate the decarboxylation. The product was then extracted into methyl *tert*-butyl

ether (2 x 22.5 mL) dried over magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil. The resulting crude oil 3.0 g was then crystallised from ethyl acetate/isohexane (1/10) to give 2-(6-chloro-pyrazin-2-yl)-3-phenyl-propionic acid **21** as a white solid, 2.2 g, 8.4 mmol, yield 68 %. Melting point: 91-92 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide-d_6): δ 12.84 (1H, s), 8.66 (1H, s); 8.52 (1H, s) 7.3-7.2 (2H, m), 7.2-7.1 (3H, m); 4.29 (1H, dd J = 9.0, 6.9Hz), 3.39 (1H, dd J = 13.9, 6.9Hz), 3.16 (1H, dd J = 13.9, 9.0Hz). ^{13}C NMR (75 MHz, dimethyl sulfoxide-d_6) δ 171.9, 154.2, 147.5, 143.3, 142.7, 138.3, 128.8, 128.2, 126.3, 51.3, 36.2. HRMS (ESI): $[M+H]^+$ calcd. for $C_{13}H_{12}N_2O_2Cl$: 263.0587, found: 263.0593. *Anal*. Calcd. for $C_{13}H_{11}N_2O_2Cl$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.49; H, 4.21; N, 10.48.

(6-Phenethyl-pyrazin-2-yl)-phenyl-amine 22. Aniline (2.1 mL, 22.8 mmol) was added to a solution of **21** (1.0 g, 3.8 mmol) in *N*-methylpyrrolidinone (10 mL) and heated to 160 °C for 20 h. The reaction mixture was purified by ion exchange column chromatography using a Varian SCX column and an eluent of methanol, followed by ammonia in methanol solution. The product containing eluent was concentrated *in vacuo* and further purified by chromatography on silica (particle size: 60A) eluting with ethyl acetate/isohexane (1/3) to give the product as a brown solid. The solid was then crystallised from ethyl acetate/ isohexane (1/10) to give a white solid 0.6 g, 2.2 mmol, yield 57 %. Melting point: 135-136 °C. ^{1}H NMR (400 MHz, dimethyl sulfoxide d_6) δ 9.36 (1H, s), 8.04 (1H, s), 7.71 (1H, s), 7.70 (2H, d J = 7.7Hz), 7.35-7.20 (6H, m), 7.2-7.1 (1H, m), 6.94 (1H, t J = 7.7Hz) 3.08-2.93 (4H, m). ^{13}C NMR (100 MHz, dimethyl sulfoxide d_6) δ 152.4, 151.6, 141.1, 140.8, 132.4, 131.9 128.7, 128.3, 128.2, 125.9, 121.1, 118.1, 35.8, 34.2. HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{18}N_3$: 276.1501, found: 276.1497. *Anal*. Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.41; H, 6.18; N, 15.00.

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