Paper

Facile Access to 1,4-Disubstituted Pyrrolo[1,2-a]pyrazines from α -Aminoacetonitriles

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(1) Clauson-Kaas reaction CN (2) Acylation (3) in situ reduction/cyclization/ aromatization



and alkvl

16 examples vields 51-68%

R = arvl, heteroarvl



Figure 1 Select pharmacologically active pyrrolo[1,2-a]pyrazine derivatives

Consequently, a variety of synthetic procedures have been developed for the preparation of pyrrolo[1,2-a]pyrazines that incorporate varied patterns of substitution.²⁻⁸ Among these, one of the oldest approaches was reported by

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Received: 12.07.2019 Accepted after revision: 16.09.2019 Published online: 01.10.2019 DOI: 10 1055/s-0039-1690699: Art ID: ss-2019-z0387-on

Abstract An efficient and practical synthetic protocol for the synthesis of 1,4-disubstituted pyrrolo[1,2-a]pyrazine derivatives is described that originates from α -substituted pyrroloacetonitriles which, in turn, are readily available from any and alkyl aldehydes. The α -pyrroloacetonitriles were subjected to a Friedel-Crafts acylation with methyl chlorooxoacetate followed by reduction of the nitrile group under Pd-catalyzed hydrogenation conditions and finally aromatization with DDQ leading to the desired pyrrolo[1,2-a]pyrazine derivatives. This method was generalized and successfully applied to various aryl, heteroaryl, and alkyl substrates. The developed protocol provides direct and convenient access to 1,4-disubstituted ring systems in moderate to good overall yields (51-68%) without the need for purification of the intermediates. Further functionalization via the stepwise halogenation (bromination, iodination) and nitration was also demonstrated. In addition, the potential of the ester functionality for elaboration was demonstrated by manipulating into heterocyclic ring systems, exemplified by conversion into benzoxazole derivatives.

Key words pyrrolo [1,2-a] pyrazine, α -aminoacetonitriles, Clauson-Kass reaction, aromatization, cyclization

Pyrrolo[1,2-a]pyrazines possess a bicyclic heteroaromatic structure that is prominent in drug design¹ associated with, for example, vasopressin 1b receptor antagonism.^{1a} dual AChE/5-HT₄ receptor antagonism,^{1b} mGluR5 antagonism,1c CK2 inhibition,1d cannabinoid receptor modulation,1e CRTH2 antagonism,1f and inhibition of sPLA-2 and hypoxia inducible factor-1^{1h} (Figure 1).

Herz and Tocker and involves the condensation of 1H-pyrrole-2-carboxaldehyde with aminoacetaldehyde diethyl acetal followed by treatment with a mixture of POCl₃ and polyphosphoric acid, a process with modest overall yields (18–24%) (Scheme 1a).² In 1996, Minguez et al. reported an improved approach that utilizes pyrrole as the starting material (Scheme 1b).³



Other routes include the cyclization between 1*H*-pyrrole-2-carboxaldehyde and a vinyl azide (Scheme 1c),⁴ a cascade route comprised of TiCl₄-catalyzed heteroatom cyclization of *N*-alkynylpyrroles under microwave irradiation conditions (Scheme 1d),⁵ and a sequence involving the reaction of 1*H*-pyrrole-2-carboxaldehyde with substituted acrylates in a Morita–Baylis–Hillman process followed by saponification and a Curtius rearrangement reaction (Scheme 1e).⁶ Palladium-catalyzed, directed C6 arylation of pyrrolo[1,2-*a*]pyrazines with a range of aryl bromides has also been reported.⁷

A need arose to access the pyrrolo[1,2-*a*]pyrazine ring system as part of a program directed toward the preparation of inhibitors of the hepatitis C virus NS5A replication complex, prompting the development of a new synthetic route that was specifically focused on the preparation of 1,4-disubstituted derivatives.⁹ Herein, we report an approach that provides direct and convenient access to this ring system starting from commercially available and inexpensive α -aminoacetonitriles.

Scheme 2 depicts a retrosynthetic analysis for the preparation of 1,4-disubstituted pyrrolo[1,2-*a*]pyrazine derivatives on which the synthetic strategy was based. An appropriate disconnection between C-1 and N-2 of 4 envisioned construction by a reductive cyclization/aromatization process conducted on a methyl 2-oxo-2-(1*H*-pyrrol-2-yl)acetate derivative **3**. In turn, **3** could be readily accessed through a Friedel–Crafts type acylation of an α -substituted 2-(1*H*-pyrrol-1-yl)acetonitrile derivative **2** with methyl chlorooxoacetate, syntheses of which have been reported in the literature as the products of a Clauson–Kaas reaction that originates with α -aminoacetonitrile derivatives **1**.





There are a number of procedures described for the synthesis of α -aminoacetonitriles.¹⁰⁻¹³ In the 1960's, α -aminoacetonitriles **1** were prepared from *N*-trimethylsilylimines (*N*-TMS imines) by reaction with cyanides.¹⁰

Hart's group¹¹ and, subsequently, Chu et al.¹² reported their elegant work on the application of *N*-TMS imines, derived from the reaction of LiHMDS with aldehydes **5**, which were treated with acetone cyanohydrin as the source of nitrile anion to generate α -aminoacetonitriles **1** (Scheme 3). The experimentally straightforward conversion of **1** to **2** was achieved under modified Clauson–Kaas reaction conditions that involved heating the α -aminoacetonitrile **1** with 2,5-dimethoxytetrahydrofuran and H₂O (1.2 mL/mmol of **1**)

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at 100 °C for 2 hours.¹⁴ This process furnished α-substituted pyrroloacetonitriles 2 in good to excellent overall yields (80-90%) (Scheme 3).15



A typical synthetic sequence for our approach, which to the best of our knowledge has not been disclosed in the literature, is illustrated by the preparation of methyl 4-phenvlpvrrolo[1,2-a]pyrazine-1-carboxylate (4a) from 2-phenvl-2-(1H-pvrrol-1-vl)acetonitrile (2a), as summarized in Scheme 4. The pyrroloacetonitrile 2a was subjected to a Friedel-Crafts acylation with methyl chlorooxoacetate followed by reduction of the nitrile group under Pd-catalyzed hydrogenation conditions. This provided the desired pyrrolo[1,2-*a*]pyrazine **4a** along with a considerable amount of **6a** (35%). Attempts to purify intermediate **6a** by a range of chromatographic methods were not successful due to its susceptibility to oxidation, which resulted in contamination with a significant amount of 4a. Although close mechanistic investigation to delineate the intermediates involved was not conducted, we hypothesize that partial reduction of the nitrile moiety to an imine followed by dehydrative cyclization affords 4a, whereas complete reduction of the nitrile to the amine results in the formation of **6a**. Although one could not rule out the possibility that **6a** could oxidize to **4a** under the reaction conditions (Pd/C), we opted to utilize an external oxidant to ensure completion of the process. Con-



Scheme 4 Synthesis of methyl 4-phenylpyrrolo[1,2-a]pyrazine-1-carboxylate (4a)

sequently, the crude reaction material from the reduction was directly treated with 2,3-dichloro-5,6-dicyano-1,4benzo-quinone (DDQ) leading to the isolation of 4a in 68% overall vield from 2a.

A broad range of α-substituted pyrroloacetonitrile derivatives **2a-p**, captured in Table 1, were synthesized and elaborated via the described protocol to access **4a-p** as a means of evaluating the scope and limitations of the process. Derivatives 4a-p were obtained from 2a-p in moderate to good overall yields that ranged from 51-68% for the three-step process.

Table 1 The Preparation of 1,4-Disubstituted Pyrrolo[1,2-a]pyrazines
 4a-p^{a-}



^a Starting materials **2** were prepared from the corresponding aldehyde by following the literature protocol as described in Scheme 3. Yields presented are overall isolated yields starting from 2.

^c Formation of only the des-bromo product **4a** rather than **4g** from **2g** was observed as the result of hydrogenolysis during the reduction.

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The halogenated products **4b-f** were isolated in 49–66% yields with the exception of the 4-bromophenyl substrate 2g, which suffered from dehalogenation during the reduction step to afford 4a in 58% overall yield rather than providing the targeted product 4g. This result provides one boundary to substituent tolerance and underscores the potential for dehalogenation under the reduction conditions involving hydrogenation over Pd/C. The other halogenated substrates, including bromide 2f, produced the targeted derivatives with negligible amounts (5-7%) of over-reduced, dehalogenated product. The differing outcomes for the regioisomeric bromides **4f** and **4g** is noteworthy since it was not anticipated. Other functional groups, including methoxyaryl (2h), hydroxymethoxyaryl (2i), and a carboxylic ester (2i), were well tolerated under the reaction conditions, providing 4h, 4i, and 4j, respectively. Substrate scope was further expanded to include heteroaromatic and aliphatic moieties, with the 3-pyridyl- and 5-indole containing substrates 2k and 2l providing 4k and 4l in 56% and 54% isolated yield, respectively. Products incorporating a cyclohexyl (**4m**), isopropyl (**4n**), and *tert*-butyl (**4o**) substituent were isolated in similar overall yields, while the unsubstituted ester 4p was obtained in 61% yield. The structure of 4b was confirmed by single crystal X-ray structural analysis, as shown in Figure 2 which revealed that the ester moiety is in-plane with the pyrrolo[1,2-a]pyrazine ring (ringester torsion angle, 1.5°) while the fluorophenyl group is twisted out of plane (ring-ring torsion angle, 52.6°).



The hydrogenation step using Pd/C as the catalyst was considered to be a limiting factor beyond dehalogenation since other functional groups of potential interest to a medicinal chemistry campaign, including alkene, alkyne, nitrile, and nitro substituents, that could serve as handles for further functionalization, would potentially be compromised. To overcome this limitation, the alternate route depicted in Scheme 5, in which the reaction sequence is rearranged, was developed. 2-(4-Bromophenyl)-2-(1*H*-pyrrol-1-yl)acetonitrile (**2g**) was selected as an illustrative example since it failed to provide the targeted product **4g** using the first protocol. Reduction of nitrile **2g** to the amine **3g** was accomplished in 90% isolated yield. Acylation of the amine of **7g** with methyl chlorooxoacetate under basic conditions afforded amide **8g**, which was subjected to dehydra-

tive cyclization in neat POCl₃ to afford **6g**. Aromatization of **6g** was accomplished by heating the crude product with DDQ to provide **4g** in 59% overall yield.



Scheme 5 Synthesis of methyl 4-(4-bromophenyl)pyrrolo[1,2-*a*]pyrazine-1-carboxylate (**4g**)

To demonstrate the potential for additional structural diversification, halogenation and nitration of **4a** were explored, with the results summarized in Schemes **6** and **7**, respectively.

Bromination of 4a using N-bromosuccinimide (NBS) in CH₂Cl₂ at room temperature for 3 hours led to the isolation of the 6-bromo derivative 9 in 73% yield accompanied by a minor amount (<5%) of the 6,8-dibromide 10 (Scheme 6). Conducting the reaction with two equivalents of NBS for 3 hours resulted in the isolation of the 6,8-dibromide 10 in 68% yield or, alternatively, exposing 9 to 1 equivalent of NBS in CH₂Cl₂ at room temperature for 3 hours gave **10** in 70% yield. The sequential nature of the halogenation allowed for alternate functionalization, with the bromide 9 affording the 6-bromo,8-iodo derivative 11 in 67% isolated yield when treated with 1 equivalent of *N*-iodosuccinimide (NIS) in DMF. The sites of halogenation were confirmed by determination of single crystal X-ray structures of 9 and 11 (Figure 3). In the solid state, the phenyl ring in both 9 and 11 adopts a more orthogonal disposition with respect to the pyrrolo[1,2-*a*]pyrazine ring (ring-ring torsion angles, 77.7° and 74.9°, respectively), compared to 4b. This may be attributed to the presence of the bromine atom at the adjacent position on the ring. While the ester group in 9 is found to approach a coplanar arrangement with the pyrrolo[1,2-a]pyrazine ring (ring-ester torsion angle = 11.8°), in 11 the ester moiety adopts an out-of-plane conformation (ring-ester torsion angle = 53.5°), presumably due to unfavorable steric effects associated with the adjacent iodine substituent.



Scheme 6 Bromination and iodination of methyl 4-phenylpyrrolo[1,2a]pyrazine-1-carboxylate (4a)



Scheme 7 Nitration of 4a

In contrast to halogenation, nitration of the pyrrolo[1,2*a*]pyrazine ring was not a selective process. Exposing **4a** to HNO_3 (1.2 equiv) and H_2SO_4 (5 equiv) at 0–5 °C for 2 hours gave a mixture of mono- (<5%), di- (30%) and trinitro (<10%) derivatives along with 39% of unreacted starting material (Scheme 7). However, by using an excess of HNO₃ (3.5 equiv) and H_2SO_4 (12 equiv) and stirring for 5 hours at room temperature, the trinitro derivative 12 was produced directly in 57% yield.17

The heavy content of NO₂ groups in **12** gave cause for concern with respect to thermal stability, which was assessed by conducting a differential scanning calorimetry (DSC) study. The results indicate that 12 is a highly energetic substance (energy 2245 J/g) with the onset of exotherm occurring at 63 °C. Compound **12** is predicted to be shock sensitive and it is strongly recommended that isolating quantities of this compound in pure form should be avoided.¹⁸

Further synthetic elaboration of 4j toward the preparation of HCV NS5A replication complex inhibitors is summarized in Scheme 8 and required manipulation of the ester moiety.⁹ Conversion of 4j to the bisphenacyl chloride 13 was accomplished by exposing to chloroiodomethane, with subsequent conversion to diester 15 by alkylation of (2S,5S)-N-Boc-5-methylpyrrolidine-2-carboxylic acid 14. Heating diester 15 with ammonium acetate in xylene at 130 °C in a sealed tube provided the bis-imidazole 16 (Scheme 8).

Elaboration of an ester functionality present in 4a to an alternate heterocycle is illustrated in Scheme 9. Saponification of 4a afforded the carboxylic acid 17, which was exposed to 2-aminophenol in the presence of propylphosphonic anhydride (PPACA, T3P®) and N,N-diisopropylethylamine (DIPEA) in EtOAc under microwave heating (150 °C)¹⁹ for 1 hour to afford 18.



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Figure 3 Single crystal X-ray structures of 9¹⁶ and 11¹⁶





In summary, we have demonstrated a new and practical synthetic protocol for the synthesis of 1,4-disubstituted pyrrolo[1,2-a]pyrazine derivatives that originates with α substituted pyrroloacetonitriles which, in turn, are readily available from aryl and alkyl aldehydes. The developed protocol provides direct and convenient access to 1.4-disubstituted ring systems in moderate to good overall yields (51-68%) without the need for purification of the intermediates. Further functionalization via the stepwise halogenation (bromination, iodination) and nitration was also demonstrated. In addition, we have demonstrated the potential of the ester functionality to be manipulated into heterocyclic ring systems by converting it to imidazole and benzoxazole derivatives. We believe these observations add further to the potential applications of pyrrolo[1,2-a]pyrazine derivatives in synthesis and drug design.

Commercially available reagents were used without additional purification, unless otherwise stated. TLC was carried out using plates coated with Kieselgel 60F254. For column chromatography, Combi-Flash chromatogram and Res-Sep Silica columns were used. NMR spectra were recorded on 300 MHz or 400 MHz spectrometer for ¹H and on 75 MHz or 100 MHz spectrometer for ¹³C at T = 300 K. NMR characterization of the isolated products was carried out in CDCl₃ or DMSO-*d*₆ at 25 °C. Chemical shifts are reported relative to the solvent residual value: $\delta = 7.26$ (CDCl₃), 2.50 (DMSO-*d*₆) for ¹H NMR and $\delta = 77.16$ (CD-Cl₃), 39.52 (DMSO- d_6) for ¹³C NMR. Resonance patterns are reported with the standard notations. In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). LCMS data were recorded on an Agilent 1200 series connected to an Agilent 6140 quadruple MS instrument. SOR was measured on a RUDOLPH Autopol® V automatic polarimeter. Compound purities were determined by analytical reversed-phase HPLC on an Agilent 1200 series instrument. Melting points were recorded using a Büchi M-560 instrument. FTIR were recorded on a Thermo Scientific iS50 FT-IR instrument. Differential scanning calorimetry (DSC) was performed on a Universal V4.5A TA Instrument. Accurate mass measurements (HRMS) were performed on an Accela UHPLC system, hyphenated with an LTO-Orbitrap XL mass spectrometer (Thermo scientific) equipped with a positive electrospray (ESI) mode.

Detailed synthetic procedures, analytical, and spectral data for all compounds **2a–p** and **4a–p** are provided in the Supporting Information.

Methyl 4-Phenylpyrrolo[1,2-a]pyrazine-1-carboxylate (4a)

(i) 2-Phenyl-2-(1H-pyrrol-1-yl)acetonitrile (2a)

In a 100 mL round-bottomed flask, 2,5-dimethoxytetrahydrofuran (0.490 mL, 3.78 mmol) was dissolved in deionized H_2O (0.6 mL, 33.3 mmol) and the reaction mixture was heated at 100 °C for 2 h. The mixture was cooled to rt, CH_2Cl_2 (2 mL), 2-amino-2-phenylacetoni-trile **1a** (500 mg, 3.78 mmol), and NaOAc (745 mg, 9.08 mmol) were added and stirring was continued for 18 h at rt. The mixture was quenched by adding sat. aq Na₂CO₃ and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), and concentrated. The crude product was purified by Combi-Flash chromatography (12 g Redi-Sep silica column; 10% EtO-Ac/PE) to afford **2a** as a colorless gummy liquid; yield: 550 mg (80%).

 ^1H NMR (300 MHz, CDCl_3): δ = 7.52–7.32 (m, 5 H), 6.83–6.75 (m, 2 H), 6.32–6.24 (m, 2 H), 6.15 (s, 1 H).

LCMS (ESI+): m/z [M + H]⁺ calcd for C₁₂H₁₀N₂: 183.1; found: 183.2

(ii) Methyl {1-[Cyano(phenyl)methyl]-1*H*-pyrrol-2-yl}(oxo)acetate (3a)

2-Phenyl-2-(1*H*-pyrrol-1-yl)acetonitrile (**2a**; 200 mg, 1.098 mmol) and methyl chlorooxoacetate (0.145 mL, 1.64 mmol) were dissolved in benzene (6 mL) and the reaction mixture was heated at 95 °C for 4 h in a 50 mL round-bottomed flask. The mixture was quenched by adding cold NaHCO₃ solution and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), and concentrated. The crude product was purified by Combi-Flash chromatography (using a 12 g Redi-Sep silica column; eluted with 10–12% EtOAc/PE) to afford **3a** as a gummy liquid; yield: 250 mg (0.930 mmol, 85%).

¹H NMR (300 MHz, CDCl₃): δ = 7.74 (s, 1 H), 7.53–7.48 (m, 1 H), 7.47–7.38 (m, 5 H), 7.30 (dd, *J* = 2.71, 1.58 Hz, 1 H), 6.42–6.38 (m, 1 H), 3.96 (s, 3 H).

LCMS (ESI–): *m*/*z* [M – H] calcd for C₁₅H₁₂N₂O₃: 267.2; found: 267.0

(iii) Methyl 4-Phenylpyrrolo[1,2-a]pyrazine-1-carboxylate (4a)

Pd/C (31.7 mg, 0.030 mmol) and AcOH (0.043 mL, 0.746 mmol) were added to a solution of **3a** (200 mg, 0.746 mmol) in MeOH (10 mL). The reaction mixture was stirred at r.t. for 4 h under 1 atm of H_2 pressure. After completion, the mixture was filtered through a bed of Celite,

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and washed with MeOH (2 × 15 mL). The solvent was evaporated to leave crude methyl 4-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-1-carboxylate (**6a**; 200 mg), which was taken as such in the next step. This material was dissolved in THF (10 mL) and DDQ (338 mg, 1.491 mmol) added. The reaction mixture was heated at 70 °C for 2 h, cooled to r.t. and quenched by adding 10% aq NaHCO₃. The mixture was extracted with EtOAc (2 × 15 mL), the combined organic layers were washed sequentially with H₂O (20 mL) and brine (20 mL), dried (Na₂SO₄), and concentrated. The crude product was purified by Combi-Flash chromatography (using a 12 g Redi-Sep silica column; eluted with 25% EtOAc/PE) to afford **4a** as yellowish gummy liquid; yield: 150 mg (0.596 mmol, 80%, after 2 steps).

FTIR: 2949.1, 1590.1, 1482.5, 1443.3, 1358.7, 1161.6, 1078.1, 1052.8, 695.3 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.70–7.62 (m, 4 H), 7.61–7.55 (m, 4 H), 7.04 (dd, *J* = 4.20, 2.64 Hz, 1 H), 4.09 (s, 3 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 159.9, 135.7, 128.2, 127.0, 126.0, 125.6, 124.8 (2 C), 124.6, 123.7, 122.8, 121.0, 112.2, 109.2, 101.8, 48.1.

LCMS (ESI+): $m/z [M + H]^+$ calcd for $C_{15}H_{12}N_2O_2$: 253.0; found: 253.0.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₅H₁₃N₂O₂: 253.0977; found: 253.0958.

Methyl 4-(4-Bromophenyl)pyrrolo[1,2-*a*]pyrazine-1-carboxylate (4g)

(i) 2-(4-Bromophenyl)-2-(1H-pyrrol-1-yl)ethan-1-amine (7g)

CoCl₂-6H₂O (228 mg, 0.957 mmol) was added to a stirred solution of 2-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)acetonitrile (**2g**; 500 mg, 1.915 mmol) in MeOH (10 mL) at 0 °C maintained under an inert atmosphere. After 10 min, NaBH₄ (362 mg, 9.57 mmol) was added in 3 equal portions to the reaction mixture over a period of 15 min, and the mixture was allowed to warm to rt and stirred for 5 h. The reaction mixture was quenched by slowly adding cold H₂O (20 mL), filtered through a bed of Celite, washed with MeOH (20 mL), and the clear filtrate concentrated under reduced pressure. The aqueous residue was extracted with EtOAc (4 × 20 mL), the combined organic layers were washed with brine (2 × 25 mL), dried (Na₂SO₄), and concentrated in vacuo to leave **7g** as a colorless gummy liquid; yield: 0.45 g (0.832 mmol, 90%).

¹H NMR (400 MHz, DMSO- d_6): δ = 7.66–7.46 (m, 2 H), 7.29–7.08 (m, 2 H), 6.89 (br s, 2 H), 6.14–5.94 (m, 2 H), 5.23–4.94 (m, 1 H), 3.24–3.08 (m, 2 H).

LCMS (ESI+): $m/z \text{ [M + H]}^+$ calcd for $C_{12}H_{13}BrN_2$: 265.0 and 267.0; found: 265.0 and 267.0

(ii) Methyl {[2-(4-Bromophenyl)-2-(1*H*-pyrrol-1-yl)ethyl]amino}(oxo)acetate (8g)

Et₃N (0.276 mL, 1.98 mmol) was added to a stirred solution of 2-(4bromophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-amine (**7g**; 350 mg, 1.32 mmol) in CH₂Cl₂ (5 mL) at 0 °C followed by the dropwise addition of methyloxalyl chloride (0.073 mL, 0.792 mmol). The mixture was warmed to rt, stirred for 4 h, diluted with CH₂Cl₂ (25 mL), and the organic layer was washed sequentially with 10% aq NaHCO₃ (20 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to leave the crude product, which was purified by Combi-Flash chromatography (using a Redi-Sep silica column and eluted with 12–15% EtOAc/PE) to give **8g** as a gummy colorless liquid; yield: 0.38 g (85%).

¹H NMR (400 MHz, DMSO- d_6): δ = 7.57–7.51 (m, 2 H), 7.22–7.17 (m, 2 H), 6.91–6.89 (m, 2 H), 6.05–6.01 (m, 2 H), 5.49–5.41 (m, 1 H), 3.99–3.80 (m, 2 H), 3.78–3.73 (m, 3 H).

LCMS (ESI+): m/z [M + H]⁺ calcd for C₁₅H₁₅BrN₂O₃: 351.0 and 352.0; found: 351.0 and 353.0.

(iii) Methyl 4-(4-Bromophenyl)pyrrolo[1,2-*a*]pyrazine-1-carboxylate (4g)

A slurry of methyl {[2-(4-bromophenyl)-2-(1H-pyrrol-1-yl)ethyl]amino}(oxo)acetate (8g; 0.3 g, 0.854 mmol) in POCl₃ (1.592 mL, 17.08 mmol) was stirred at rt for 12 h. The reaction mixture was concentrated under vacuum to remove the POCl₃ and the residue was diluted with EtOAc (20 mL) and washed with 10% aq NaHCO₃ (20 mL) followed by brine $(2 \times 20 \text{ mL})$. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to leave crude methyl 4-(4bromophenyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-1-carboxylate(6g) as a brown solid (260 mg). This intermediate was characterized by LCMS. [LCMS (ESI+): m/z [M + H]⁺ calcd for C₁₅H₁₃BrN₂O₂: 333.1 and 335.1; found: 333.1 and 335.1]. DDQ (338 mg, 1.491 mmol) was added to a solution of the crude material in THF (10 mL) and the mixture heated at 70 °C for 2 h. The mixture was quenched by adding 10% aq NaHCO₃ and extracted with EtOAc (2×25 mL). The combined organic layers were washed sequentially with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by Combi-Flash chromatography (using a 12 g Red-Sep silica column and the product eluted with 22-25% EtOAc/PE) to afford 4g as a colorless gummy liquid; yield: 0.21 g (0.657 mmol, 77% after 2 steps).

 ^1H NMR (400 MHz, DMSO- $d_6):$ δ = 7.88–7.71 (m, 5 H), 7.70–7.63 (m, 1 H), 7.45–7.36 (m, 1 H), 7.17–7.09 (m, 1 H), 3.97 (s, 3 H).

 13 C NMR (100 MHz, DMSO- d_6): δ = 164.7, 140.8, 132.8, 131.7, 131.1, 130.7, 127.3, 126.2, 124.2, 117.6, 114.8, 106.3, 53.0.

LCMS (ESI+): m/z [M + H]⁺ calcd for $C_{15}H_{11}BrN_2O_2$: 331.0 and 333.0; found: 331.0 and 333.0.

HRMS (ESI): m/z [M + H]⁺ calcd for $C_{15}H_{12}BrN_2O_2$: 331.0082 and 333.0062; found: 331.0088 and 333.0065.

Methyl 6-Bromo-4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (9)

NBS (31.7 mg, 0.178 mmol) was added to a solution of methyl 4phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (**4a**; 90 mg, 0.357 mmol) in CH₂Cl₂ (5 mL) maintained at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, quenched by the addition of H₂O, and the mixture extracted with EtOAc (2×25 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude material was purified by preparative HPLC to afford **9** as a yellow solid; yield: 86 mg (0.260 mmol, 73%); mp 164 °C.

¹H NMR (400 MHz, CD₃OD): δ = 7.69 (d, J = 4.6 Hz, 1 H), 7.60–7.41 (m, 6 H), 7.06–7.00 (m, 1 H), 4.16–3.98 (m, 3 H).

 ^{13}C NMR (75 MHz, CD₃OD): δ = 163.9, 133.3, 131.1, 130.4, 129.6, 129.3, 127.9, 127.4, 122.2, 108.4, 52.0.

LCMS (ESI+): m/z [M + H]⁺ calcd for $C_{15}H_{11}BrN_2O_2$: 331.1 and 333.1; found: 331.2 and 333.2.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₅H₁₂BrN₂O₂: 331.0082 and 333.0062; found: 331.0084 and 333.0065.

Methyl 6,8-Dibromo-4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (10)

NBS (70.6 mg, 0.396 mmol) was added to a solution of methyl 4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (**4a**; 100 mg, 0.396 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 3 h, diluted with H₂O, and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄) and concentrated under vacuum. The crude product was purified by preparative HPLC to afford **10** as an off-white solid; yield: 110.5 mg (0.269 mmol, 68%); mp 169.5 °C.

¹H NMR (400 MHz, DMSO- d_6): δ = 7.60–7.50 (m, 5 H), 7.48–7.46 (m, 1 H), 7.41–7.40 (m, 1 H), 4.00 (s, 3 H).

 ^{13}C NMR (75 MHz, DMSO- d_6): δ = 164.5, 144.5, 131.4, 130.6, 130.4, 129.8, 127.6, 123.6, 123.1, 98.1, 91.4, 52.9.

LCMS (ESI+): m/z [M + H]⁺ calcd for C₁₅H₁₀Br₂N₂O₂: 410.0; found: 411.0.

HRMS (ESI): $m/z \ [M + H]^+$ calcd for $C_{15}H_{11}Br_2N_2O_2$: 410.9167; found: 410.9164.

Methyl 6-Bromo-8-iodo-4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (11)

NIS (82 mg, 0.362 mmol) was added to a solution of methyl 6-bromo-4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (**9**; 120 mg, 0.362 mmol) in DMF (5 mL) and the mixture stirred at rt for 3 h. The mixture was quenched by adding H₂O and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated under vacuum. The crude material was purified by preparative HPLC to furnish **11** as a white solid; yield: 111 mg (0.242 mmol, 67%); mp 178 °C.

 ^1H NMR (400 MHz, DMSO- $d_6):$ δ = 7.59–7.50 (m, 5 H), 7.46–7.44 (m, 1 H), 7.41 (s, 1 H), 4.08–3.98 (m, 3 H).

¹³C NMR (75 MHz, DMSO- d_6): δ = 165.0, 146.0, 132.2, 131.9, 131.1, 130.3, 129.2, 129.1, 128.3, 128.1, 126.6, 99.7, 59.5, 53.3.

LCMS (ESI+): m/z [M + H]⁺ calcd for C₁₅H₁₀BrIN₂O₂: 456.9 and 457.9; found: 456.9 and 457.8.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₅H₁₁BrIN₂O₂: 456.9049 and 458.9028; found: 456.9043 and 458.9020.

Methyl 6,8-Dinitro-4-(4-nitrophenyl)pyrrolo[1,2-*a*]pyrazine-1-carboxylate (12)

Methyl 4-phenylpyrrolo[1,2-*a*]pyrazine-1-carboxylate (**4a**; 100 mg, 0.396 mmol) was added to concentrated H_2SO_4 (211 µL, 3.96 mmol) and the mixture cooled to 0 °C. Concentrated HNO₃ (53.1 µL, 1.189 mmol) was added and the mixture warmed to rt and stirred for 5 h. The crude reaction mixture was quenched by adding ice cold H_2O , extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed under vacuum and the crude material purified by preparative HPLC to afford **12** as a light yellow colored solid; yield: 87 mg (0.224 mmol, 57%); mp 71 °C (dec., turned gummy black).

 ^1H NMR (400 MHz, DMSO- d_6): δ = 8.98–8.92 (m, 1 H), 8.84–8.78 (m, 1 H), 8.32–8.24 (m, 1 H), 7.83–7.76 (m, 1 H), 7.73 (s, 1 H), 7.69–7.65 (m, 1 H), 7.44–7.40 (m, 1 H), 7.31–7.31 (m, 1 H), 7.15–7.12 (m, 1 H), 4.01–3.95 (m, 3 H).

 ^{13}C NMR (75 MHz, DMSO- d_6): δ = 163.7, 148.27, 147.98, 144.19, 138.04, 135.9, 133.4, 131.9, 131.0, 127.3, 127.1, 124.3, 122.1, 120.8, 117.3, 53.3.

LCMS (ESI+): m/z calcd $[M + H]^+$ for $C_{15}H_9N_5O_8$: 387.2; found: 388.0.

HRMS (ESI): m/z [M + H]⁺ calcd for $C_{15}H_{10}N_5O_8$: 388.0529; found: 388.0524.

2-(4-Phenylpyrrolo[1,2-a]pyrazin-1-yl)benzo[d]oxazole (18)

Compound **18** was prepared from the intermediate acid **17** (85 mg, 0.356 mmol) by following a literature protocol¹⁹ using T3P and DIPEA in EtOAc at 150 °C under microwave condition for 1 h; light brown gummy liquid; yield: 48 mg (0.154 mmol, 43%).

 ^1H NMR (400 MHz, CDCl_3): δ = 8.04–8.00 (m, 1 H), 7.96–7.91 (m, 1 H), 7.78–7.68 (m, 5 H), 7.64–7.54 (m, 3 H), 7.50–7.40 (m, 2 H), 7.11–7.05 (m, 1 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 159.9, 150.7, 142.0, 132.0, 131.9, 130.2 (3 C), 129.3 (3 C), 126.6, 126.5, 126.3, 124.9, 121.0, 116.7, 114.2, 111.2, 106.9.

LCMS (ESI+): m/z [M + H]⁺ calcd for C₂₀H₁₃N₃O: 312.2; found: 312.2.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₄N₃O: 312.1137; found: 312.1140.

Acknowledgment

The authors express their appreciation to the Department of Discovery Analytical Sciences (DAS) for analytical support and Analytical Research and Development (ARD), Biocon Bristol-Myers Squibb Research Centre, Bangalore, India for X-ray diffraction (XRD) analysis of the samples.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690699.

References

- (1) (a) Arban, R.; Bianchi, F.; Buson, A.; Cremonesi, S.; Fabio, R. D.; Gentile, G.; Micheli, F.; Pasquarello, A.; Pozzan, A.; Tarsi, L.; Terreni, S.; Tonelli, F. Bioorg. Med. Chem. Lett. 2010, 20, 5044. (b) Lecoutey, C.; Rochais, C.; Genest, D.; Butt-Gueulle, S.; Ballandonne, C.; Corvaisier, S.; Dulin, F.; Lepailleur, A.; Sopkova-De, O.; Santos, J.; Dallemagne, P. Med. Chem. Commun. 2012, 3, 627. (c) Micheli, F.; Bertani, B.; Bozzoli, A.; Crippa, L.; Cavanni, P.; Di Fabio, R.; Donati, D.; Marzorati, P.; Merlo, G.; Paio, A.; Perugini, L.; Zarantonello, P. Bioorg. Med. Chem. Lett. 2008, 18, 1804. (d) Guillon, J.; Le Borgne, M.; Rimbault, C.; Moreau, S.; Savrimoutou, S.; Pinaud, N.; Baratin, S.; Marchivie, M.; Roche, S.; Bollacke, A.; Pecci, A.; Alvarez, L.; Desplat, V.; Jose, J. Eur. J. Med. Chem. 2013, 65, 205. (e) Eatherton, A. J.; Giblin, M. P.; Mitchell, W. L. Patent WO 2007/088168 A1, 2007. (f) Vidal, J. B.; Alonso-Diez, J. A.; Buil Albero, M. A.; Eastwood, P. R.; Esteve Trias, C.; Lozoya Toribio, M. E.; Roberts, R. S.; Vidal Gisbert, L.; Conzalez Rodriguez, J.; Mir Cepeda, M. Patent WO 2013/010880, 2013. (g) Ohtani, M.; Fuji, M.; Okada, T. Patent US 6407104 B1, 1999. (h) Fleury, M. B.; Largeron, M. Tetrahedron 1985, 41, 3705.
- (2) (a) Herz, W.; Tocker, S. J. Am. Chem. Soc. **1955**, 77, 6353. (b) Herz, W.; Tocker, S. J. Am. Chem. Soc. **1955**, 77, 6355.
- (3) Minguez, J. M.; Castellote, M. I.; Vaquero, J. J.; Garcia-Navio, J.; Builla, J. A.; Castano, O. J. Org. Chem. 1996, 61, 4655.
- (4) Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. Org. Lett. 2010, 12, 3863.
- (5) Alfonsi, M.; Acqua, D. M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. Eur. J. Org. Chem. 2009, 74, 2852.

L

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- (6) Nayak, M.; Pandey, G.; Batra, S. Tetrahedron 2011, 67, 7563.
- (7) Park, S.; Jung, Y.; Kim, I. *Tetrahedron* **2014**, 70, 7534.
- (8) (a) Shvedov, V. I.; Altukhova, L. B.; Grinev, A. N. Chem. Heterocycl. Compd. 1970, 6, 975. (b) Chu, X.; Zhang, Z.; Wang, C.; Chen, X.; Wang, B.; Ma, C. Tetrahedron 2017, 73, 7185. (c) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. Tetrahedron 2008, 64, 6876. (d) Wan, W.; Xu, X.; Chen, Y.; Jiang, H.; Wang, Y.; Deng, H.; Hao, J. Eur. J. Org. Chem. 2017, 3145. (e) Yuan Liu, Y.; Yu, Y.; Fu, Y.; Liu, Y.; Shi, L.; Li, H.; Wang, W. Org. Chem. Front. 2017, 4, 2119. (f) Shao, N.; Li, J.; Zhu, H.; Zhang, S.; Zou, H. Tetrahedron 2018, 74, 6088. (g) Liu, H.; Zhou, F.; Luo, W.; Chen, Y.; Zhanga, C.; Ma, C. Org. Biomol. Chem. 2017, 15, 6076. (h) Guven, S.; Ozer, M. S.; Kaya, S.; Menges, N.; Balci, M. Org. Lett. 2015, 17, 2660. (i) Ozer, M. S.; Menges, N.; Keskin, S.; Sahin, E.; Balci, M. Org. Lett. 2016, 18, 408.
- (9) Belema, M.; Pothukanuri, S.; Bender, J. A.; Lopez, O. D.; Chen, Q.; Rampulla, R. A.; Gupta, S. A. K.; Meanwell, N. A. Patent WO 2012/21591 A1, **2012**.
- (10) (a) Kruger, C.; Rochow, E. G.; Wanngat, U. Chem. Ber. 1963, 96, 2132. (b) Chan, L.-H.; Rochow, J. J. Organomet. Chem. 1967, 9, 231.
- (11) (a) Hart, D. J.; Kanai, K. J. Org. Chem. 1982, 47, 1555. (b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. J. Org. Chem. 1983, 48, 289. (c) Hart, D. J.; Hong, W-P.; Hsu, L-Y. J. Org Chem. 1987, 52, 4665.

Paper

- (12) Guo-Ha, C.; Gu, M.; Gerared, B.; Dolle, R. E. Synth. Commun. **2004**, 34, 4583.
- (13) (a) Bhanu Prasad, V. A.; Bisai, A.; Singh, V. K. Tetrahedron Lett.
 2004, 45, 9565. (b) Harusawa, S.; Hamada, Y.; Shioiri, T. Tetrahedron Lett. 1979, 20, 4663.
- (14) (a) Gourlay, B. S.; Molesworth, P. P.; Ryanb, J. H.; Smith, J. A. Tetrahedron Lett. **2006**, 47, 799. (b) Kucukdisli, M.; Opatz, T. J. Org. *Chem.* **2013**, 78, 6670.
- (15) (a) Strecker, A. Ann. Chem. Pharm. **1850**, 75, 27. (b) Strecker, A. Ann. Chem. Pharm. **1854**, 91, 349.
- (16) CCDC 1897797 (compound 4b), CCDC 1897798 (compound 9), CCDC 1897799 (compound 11) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
- (17) Terenin, V. I.; Butkevich, M. A.; Pleshkova, A. P. Chem. Heterocycl. Compd. 2005, 41, 1327.
- (18) Differential scanning calorimetry (DSC) data/spectra are provided in the Supporting Information.
- (19) Xiaoan, W. X.; Bakali, J. E.; Deprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2012**, 53, 2440.