Note

A flexible strategy for the regiocontrolled synthesis of pyrazolo[1,5-a]pyrazines

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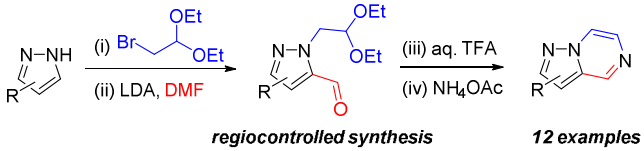
A flexible strategy for the regiocontrolled synthesis of pyrazolo[1,5-*a*]pyrazines

Peter J. Lindsay-Scott,* Natalie G. Charlesworth, Alexandru Grozavu

Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, Surrey GU20 6PH, United Kingdom

Supporting Information Placeholder

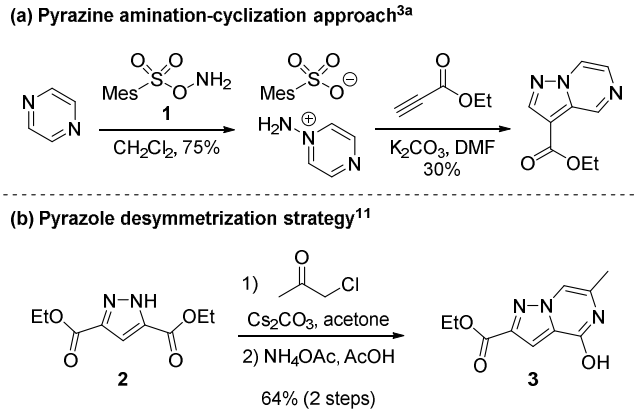


ABSTRACT: A 4 step protocol for the synthesis of pyrazolo[1,5-*a*]pyrazines has been developed. Commercially available pyrazoles were alkylated and formylated in a regiocontrolled manner to give pyrazole-5-aldehydes bearing 2,2-dialkoxyethyl substitution on *N*-1. Efficient conditions for the subsequent deprotection and cyclization of these intermediates allowed access to pyrazolo[1,5-*a*]pyrazines with multiple substitution patterns. The versatility of the pyrazole-5-aldehyde intermediates was further demonstrated through a deprotection and double-reductive amination sequence to give 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazines.

Nitrogen-containing heterocycles are ubiquitous in modern drug discovery.[1] Medicinal chemistry teams frequently incorporate nitrogen atoms in aromatic and heteroaromatic ring systems to modulate key physicochemical properties such as lipophilicity, polarity and hydrogen-bonding ability in their pursuit of new pharmacological agents.[2] In recent years, pyrazolo[1,5-*a*]pyrazines have emerged as an important class of nitrogen heterocycles. They have been investigated in a variety of biological settings, including as kinase inhibitors (against JAK,[3a] GSK3,[3b] PI3K[3c] and CHK-1[3d] kinases), dopamine receptor agonists[4], V1b antagonists[5] and Orexin receptor antagonists.[6]

Synthetic strategies towards pyrazolo[1,5-*a*]pyrazines have largely focused on building up the pyrazole ring from pyrazine precursors (Scheme 1a). Using this methodology, 3-substituted pyrazolo[1,5-*a*]pyrazines can be accessed in low yields via the intermolecular reaction of *N*-aminopyrazinium salts and alkynes,[3a] whilst the corresponding 6-substituted analogues can be synthesized via intramolecular gold- and silver-catalyzed variants.[7] A Pd-mediated tandem C-H functionalization-cyclization tactic has also been explored by Charette and co-workers to construct 2-substituted pyrazolo[1,5-*a*]pyrazines.[8] These approaches suffer from several drawbacks, including the use of thermally-hazardous *N*-amination reagents (e.g. *O*-mesitylenesulfonyl hydroxylamine **1**)[9] to prepare the requisite *N*-aminopyrazinium starting materials and a limited reported substrate scope. An alternative synthetic approach towards pyrazolo[1,5-*a*]pyrazines that has received relatively little attention from the synthetic community involves building up the pyrazine ring from pyrazole precursors.[6,10] Using this strategy, Karp and co-workers were able to form pyrazolo[1,5-*a*]pyrazine **3** in 64% yield over 2 steps via the desymmetrization of pyrazole diester **2** (Scheme 1b).[11] The products from this desymmetrization approach necessarily contain an ester group in the 2-position, but this can be excised via decarboxylation at high temperature.[12] However, despite these advances, no general method has been reported to date which is capable of providing flexible access to pyrazolo[1,5-*a*]pyrazines bearing multiple substitution patterns in high yields.

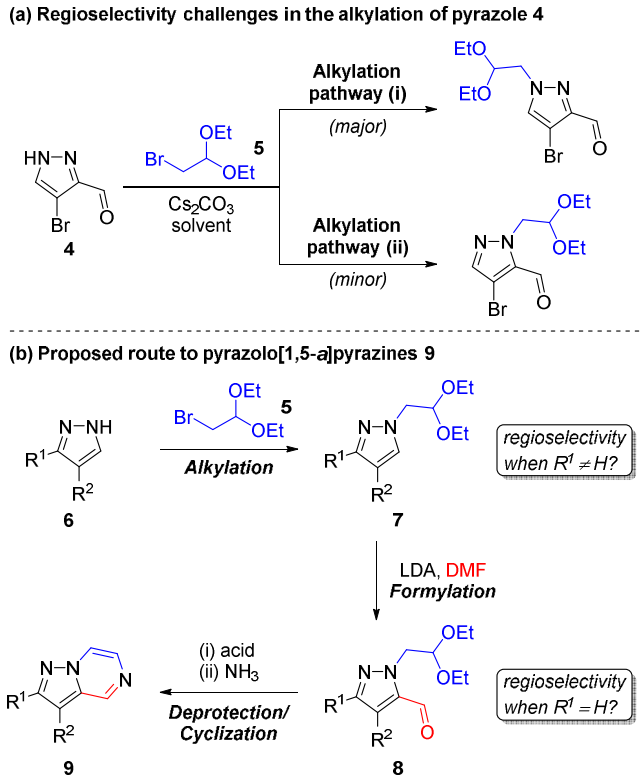
Scheme 1. Synthetic strategies towards pyrazolo[1,5-*a*]pyrazines



We wondered whether pyrazoles **8** bearing an aldehyde at the 5-position and a 2,2-dialkoxyethyl group on *N*-1 might serve as versatile intermediates for the construction of pyrazolo[1,5-*a*]pyrazines (Scheme 2). In order to investigate this hypothesis, we required synthetic access to these intermediates in a regiocontrolled manner. To this end, we investigated the alkylation of commercially available pyrazole **4** with alkyl bromide **5** in a range of solvents in order to assess the alkylation regioselectivity (Scheme 2a). However, the major product observed in all cases was the undesired regioisomer formed through alkylation pathway (i) (see the Supporting Information). These observations are in accordance with literature precedent,[13] which suggests that the alkylation of 3- and 3,4-

substituted pyrazoles generally leads to mixtures of regioisomeric products favoring the *N*-1 alkylated isomer.

Scheme 2. Pyrazole alkylation regioselectivity challenges and proposed route to pyrazolo[1,5-*a*]pyrazines 9

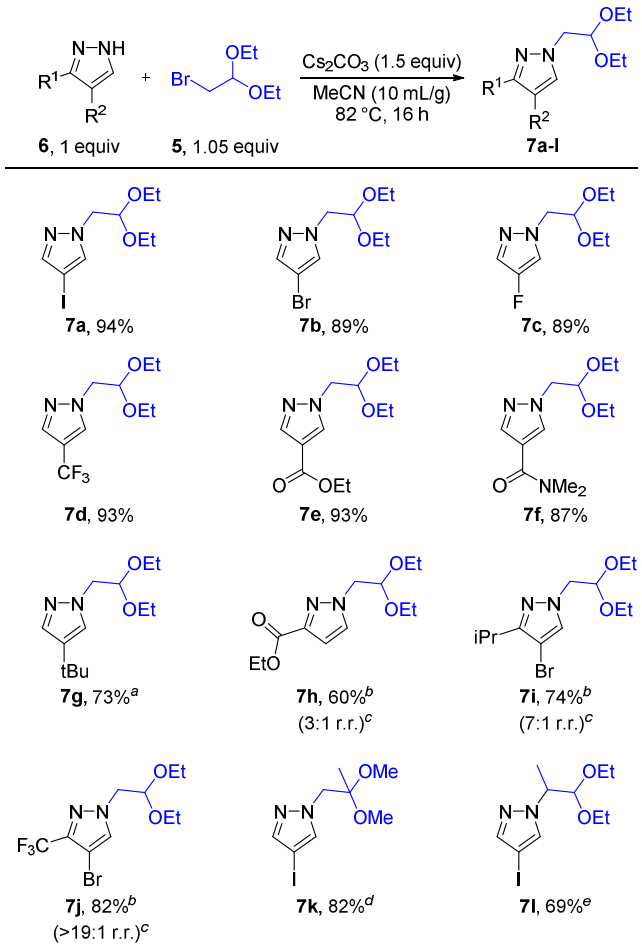


In order to overcome these regioselectivity issues, we opted instead to explore an alkylation-formylation strategy (Scheme 2b). Encouraged by reports of the selective metalation of *N*-1 alkylated pyrazoles at the 5-position,[14] we were intrigued by the possibility of using a 2,2-dialkoxyethyl group on nitrogen to both control the regiochemistry of formylation and to serve as a useful functional handle for further elaboration.[15] We reasoned that the alkylation of either tautomer of 4-substituted pyrazoles **6** (R^1 = H) would lead to identical alkylated products **7**, which might then undergo regioselective metalation at the most acidic 5-position.[14] In contrast, the alkylation of 3- and 3,4-substituted pyrazoles **6** ($R^1 \neq$ H) would be expected to generate *N*-1 alkylated pyrazoles **7** regioselectively, allowing subsequent metalation at the remaining 5-position. We hypothesized that the acid-mediated deprotection of key intermediates **8** and subsequent ring closure with ammonia would then furnish the target heterocycles **9**.

A range of commercially available pyrazoles **6** were therefore subjected to alkylation with alkyl bromide **5** (Scheme 3). While 4-substituted pyrazoles were alkylated smoothly without any issues of regioselectivity (see **7a-g**), the alkylation of pyrazoles bearing substituents in the 3-position generated mixtures of regiosomeric products. Gratifyingly, the desired alkylated isomer was formed predominantly in all cases and the regioisomeric mixtures were readily separable by column chromatography.[16] The synthesis of pyrazoles **7k** and **7l** bearing methyl substituents on the alkyl chain required more forcing alkylation conditions.

With a range of alkylated pyrazoles **7a-l** in hand, we set out to explore the formylation step (Scheme 4). Thus, deprotonation of 4-substituted pyrazoles **7a-f** with LDA at low temperature followed by addition of DMF allowed access to pyrazole-aldehydes **8a-f** in a regioselective manner, with formylation occurring exclusively at the 5-position (75-89% yield).[16] Despite substitution on the 2,2-dialkoxyethyl group, pyrazoles **8k** and **8l** were also formed in high yields. Moreover, subjection of 3-substituted pyrazoles **7h-j** to the formylation conditions delivered the corresponding pyrazole-aldehydes **8h-j** as single regioisomers. However, *t*-Bu-substituted pyrazole **7g** failed to show any conversion of starting material to the desired product **8g** under the reaction conditions. Interestingly, some elimination of ethanol from the 2,2-dialkoxyethyl group was observed during the formylation of ester-containing substrates **7e** and **7h** (see the Experimental section).

Scheme 3. Alkylation of pyrazoles 6

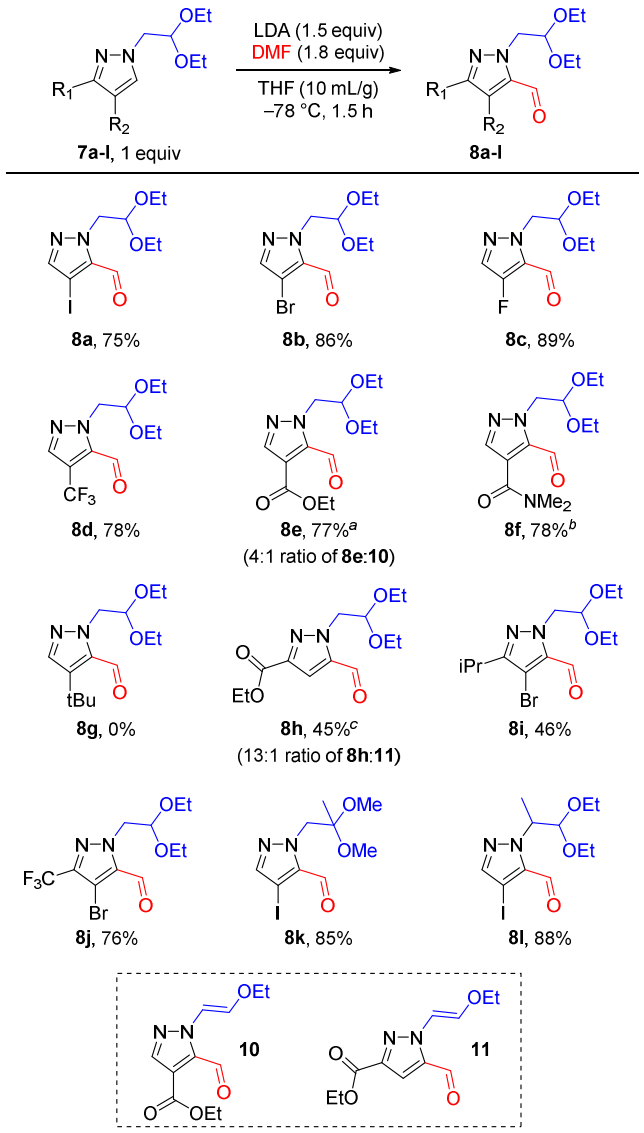


[a]Cs_2CO_3 (3 equiv), **5** (1.25 equiv), MeCN, 82 °C. [b]Yield of pure isolated regioisomer after chromatography. [c]Regioselectivity reported in parentheses was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]1-bromo-2,2-dimethoxypropane (1.05 equiv), Cs_2CO_3 (1.5 equiv), DMSO, 120 °C. [e]2-bromo-1,1-diethoxypropane (2 equiv), Cs_2CO_3 (6 equiv), DMSO, 120 °C.

Having prepared the key intermediates **8** in a regiocontrolled fashion, we turned our attention to the acid-mediated acetal deprotection step and subsequent ring closure with ammonia (Scheme 5). Unfortunately, our initial attempts to effect this transformation in a one-pot manner with ammonia sources in the presence of ethanol and acetic acid gave rise to complex reaction mixtures. However, we were delighted to find that an alternative 2 step deprotection-cyclization protocol provided

the target pyrazolo[1,5-*a*]pyrazines **9** in high yields (Scheme 5). Thus, acetal deprotection of pyrazoles **8** with aqueous TFA[17] followed by solvent swapping and subsequent cyclization with ammonium acetate furnished the desired products **9**, circumventing the need to isolate the dialdehyde intermediates.[18]

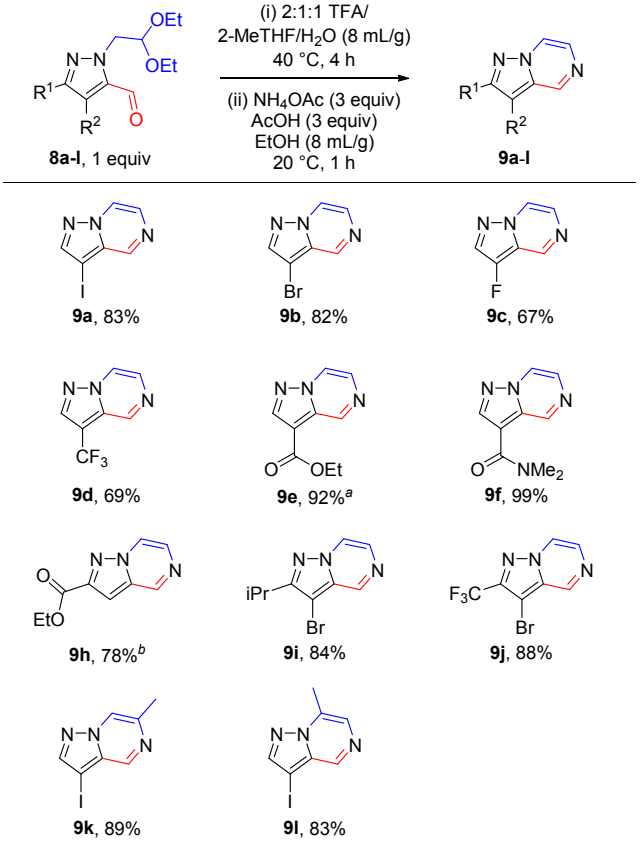
Scheme 4. Formylation of alkylated pyrazoles 7



[a]Material contained compound **10** as an impurity after flash chromatography. [b]2.0 equiv LDA used. [c]Material contained compound **11** as an impurity after flash chromatography.

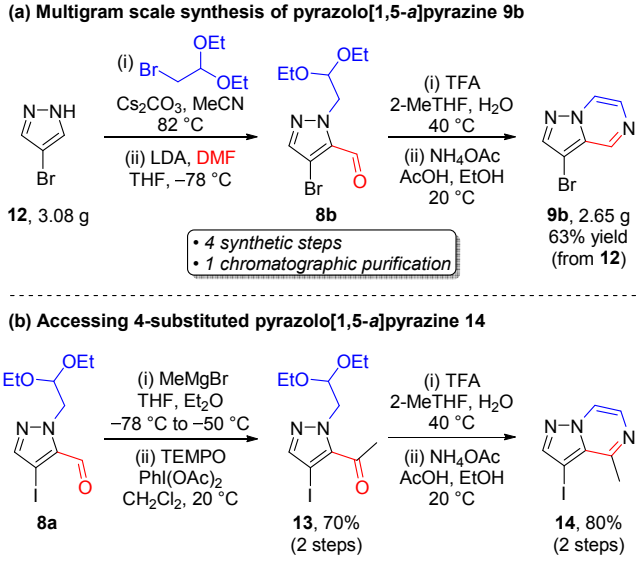
Next, in order to probe the robustness and scalability of the synthetic methodology, we subjected bromopyrazole **12** to the alkylation, formylation, deprotection and cyclization protocols on multigram scale (Scheme 6a). Thus, pyrazolo[1,5-*a*]pyrazine **9b** was furnished in 63% yield over 4 steps, with only a single chromatographic purification performed at the end of the synthetic sequence. With access secured to pyrazolo[1,5-*a*]pyrazines bearing substitution at the 2-, 3-, 6- and 7-positions, we then investigated the formation of a 4-substituted analogue (Scheme 6b). Thus, addition of MeMgBr to pyrazole **8a** and subsequent oxidation delivered ketone **13** in 70% yield over 2 steps, which was subjected to the standard deprotection-cyclization sequence to give pyrazolo[1,5-*a*]pyrazine **14** in 80% yield over 2 steps.

Scheme 5. Formation of pyrazolo[1,5-*a*]pyrazines 9



[a]Starting material contained compound **10** as an impurity. [b]Starting material contained compound **11** as an impurity.

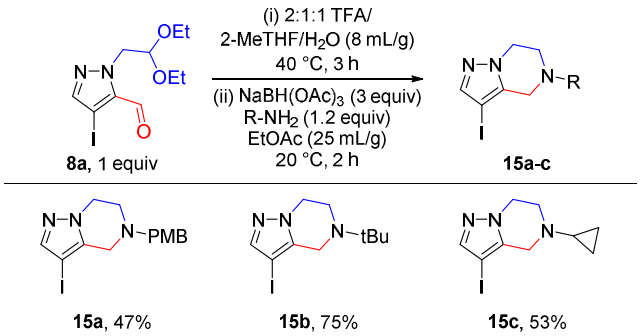
Scheme 6. Multigram scale synthesis of 9b and further synthetic transformations of pyrazole-aldehyde 8a



Finally, we explored the synthesis of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazines from pyrazole **8a** (Scheme 7). These structurally-related compounds represent an important class of heterocycles with widespread applications in

medicinal chemistry.[19] A deprotection and double-reductive amination process was therefore developed, giving rise to saturated analogues **15a-c** in yields of 47-75% over 2 steps.

Scheme 7. A double-reductive amination approach to 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazines 15



In summary, we have developed a flexible strategy for the synthesis of pyrazolo[1,5-*a*]pyrazines. The regioselectivity challenges, low yields and thermally-hazardous reagents associated with existing synthetic methodologies have been successfully overcome via a 4 step reaction sequence. Furthermore, the pyrazole-5-aldehyde intermediates were shown to be amenable to functionalization, allowing access to multiple substitution patterns and saturated analogues in a highly regiocontrolled manner.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of N_2 and commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on commercially available pre-coated TLC plates (0.25 mm silica gel with fluorescent indicator UV254) and visualisation was achieved by either the quenching of UV fluorescence or with a $KMnO_4$ stain. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AV-HD 400 spectrometer and Bruker Avance III 500 spectrometer. Signal positions were recorded in δ ppm with the abbreviations s, br. s, d, t, q, quint, dd and m denoting singlet, broad singlet, doublet, triplet, quartet, quintet, doublet of doublets and multiplet respectively. All ^1H NMR chemical shifts were referenced to $SiMe_4$ as an internal standard (0.00 ppm). All ^{13}C NMR chemical shifts in $CDCl_3$ were referenced to the residual solvent peak at 77.00 ppm. All ^{19}F NMR chemical shifts were referenced to $CFCl_3$ (0.00 ppm). All coupling constants, *J*, are quoted in Hz. Infra-red spectra were recorded on a Shimadzu IRAffinity 1 FT-IR spectrometer. Melting points were obtained using a DSC 1 STARe system. High-resolution electrospray ionization (ESI-TOF) mass spectra were obtained with an Agilent Technologies 6230 series time-of-flight mass spectrometer.

General Procedure 1 for alkylation of pyrazoles. To a stirred solution of the pyrazole **6** (1 equiv.) in acetonitrile (8 mL/g) at room temperature was added cesium carbonate (1.5 equiv.) in one portion, followed by a solution of 2-bromo-1,1-diethoxy-ethane 5 (1.05 equiv.) in acetonitrile (2 mL/g) dropwise. The reaction mixture was stirred in an 82 °C heating block for 16 hours, then was cooled to room temperature and filtered through celite, washing with ethyl acetate (20 mL/g). The filtrate was concentrated to give a residue which was purified as specified.

1-(2,2-Diethoxyethyl)-4-iodo-1*H*-pyrazole (7a). 4-Iodo-1*H*-pyrazole (1.02 g, 5.28 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7a** (1.54 g, 4.99 mmol, 94% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2974, 1121, 1055, 941; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, s), 7.50 (1H, s), 4.72 (1H, t, *J* 5.5), 4.20 (2H, d, *J* 5.5), 3.74-3.66 (2H, m), 3.47-3.39 (2H, m), 1.16 (6H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 144.5, 134.9, 101.2, 63.7, 55.8, 55.4, 15.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{15}IN_2O_2$ 310.0178; Found 310.0180.

4-Bromo-1-(2,2-diethoxyethyl)-1*H*-pyrazole (7b). 4-Bromo-1*H*-pyrazole (0.993 g, 6.76 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7b** (1.59 g, 6.06 mmol, 89% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2976, 1122, 1055, 953; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, s), 7.46 (1H, s), 4.72 (1H, t, *J* 5.4), 4.17 (2H, d, *J* 5.3), 3.74-3.66 (2H, m), 3.48-3.40 (2H, m), 1.17 (6H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 140.0, 130.6, 101.1, 92.9, 63.7, 55.6, 15.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{15}BrN_2O_2$ 262.0317; Found 262.0316.

1-(2,2-Diethoxyethyl)-4-fluoro-1*H*-pyrazole (7c). 4-Fluoro-1*H*-pyrazole (0.800 g, 9.23 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7c** (1.67 g, 8.29 mmol, 89% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2978, 1580, 1126, 1061, 1020; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, d, *J* 4.1), 7.34 (1H, d, *J* 4.1), 4.71 (1H, t, *J* 5.3), 4.10 (2H, d, *J* 5.3), 3.74-3.66 (2H, m), 3.48-3.41 (2H, m), 1.18 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 149.5 (d, *J* 245.0), 126.4 (d, *J* 13.9), 116.6 (d, *J* 27.9), 101.3, 63.7, 55.9, 15.2; δ_F (^1H decoupled, 376 MHz, $CDCl_3$) −177.5; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{15}FN_2O_2$ 202.1118; Found 202.1110.

1-(2,2-Diethoxyethyl)-4-(trifluoromethyl)-1*H*-pyrazole (7d). 4-(Trifluoromethyl)-1*H*-pyrazole (0.570 g, 4.19 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7d** (0.987 g, 3.91 mmol, 93% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2980, 1238, 1115, 1057, 968; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, s), 7.70 (1H, s), 4.75 (1H, t, *J* 5.4), 4.22 (2H, d, *J* 5.3), 3.76-3.68 (2H, m), 3.48-3.40 (2H, m), 1.16 (6H, t, *J* 7.1); δ_C (100 MHz, $CDCl_3$) 137.1, 130.0 (q, *J* 3.7), 122.6 (q, *J* 266.3), 113.6 (q, *J* 38.2), 101.0, 63.9, 55.4, 15.1; δ_F (^1H decoupled, 376 MHz, $CDCl_3$) −56.4; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{15}F_3N_2O_2$ 252.1086; Found 252.1075.

Ethyl 1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylate (7e). Ethyl 1*H*-pyrazole-4-carboxylate (1.12 g, 7.98 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7e** (1.90 g, 7.43 mmol, 93% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2978, 1715, 1554, 1225, 1113, 1059, 1026; δ_H (400 MHz, $CDCl_3$) 7.95 (1H, s), 7.91 (1H, s), 4.78 (1H, t, *J* 5.3), 4.29 (2H, q, *J* 7.2), 4.20 (2H, d, *J* 5.3), 3.75-3.67 (2H, m), 3.48-3.41 (2H, m), 1.35 (3H, t, *J* 7.2), 1.16 (6H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 163.0, 141.2, 133.9, 115.1, 100.9, 63.7, 60.1, 55.3, 15.1, 14.3; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{20}N_2O_4$ 256.1423; Found 256.1420.

1-(2,2-Diethoxyethyl)-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide (7f). *N*,*N*-Dimethyl-1*H*-pyrazole-4-carboxamide (0.485 g, 3.49 mmol) was subjected to General Procedure 1. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-10% methanol/ethyl acetate) to give pyrazole **7f** (0.779 g, 3.05 mmol, 87% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2976, 1609, 1551, 1123, 1057; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, s), 7.74 (1H, s), 4.78 (1H, t, *J* 5.3), 4.20 (2H, d, *J* 5.3), 3.75-3.67 (2H, m), 3.49-3.41 (2H, m), 3.19 (3H, br. s), 3.10 (3H, br. s), 1.16 (6H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 164.4, 139.8, 132.7, 117.3, 100.9, 63.5, 55.0, 38.8, 35.8, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{21}N_3O_3$ 255.1583; Found 255.1577.

4-(*tert*-Butyl)-1-(2,2-diethoxyethyl)-1*H*-pyrazole (7g). To a stirred solution of 4-*tert*-butyl-1*H*-pyrazole (0.504 g, 4.05 mmol) in acetonitrile (4.03 mL) at room temperature was added cesium carbonate (1.99 g, 6.09 mmol) in one portion, followed by a solution of 2-bromo-1,1-diethoxyethane (0.661 mL, 4.26 mmol) in acetonitrile (1.01 mL) dropwise. The reaction mixture was stirred in an 82 °C heating block for 16 hours. To the mixture was added cesium carbonate (1.99 g, 6.09 mmol) in one portion, followed by a solution of 2-bromo-1,1-diethoxyethane (0.126 mL, 0.811 mmol) in acetonitrile (0.50 mL) dropwise. The reaction mixture was stirred in an 82 °C heating block for 2 hours, then was cooled to room temperature and filtered through celite, washing with ethyl acetate (100 mL). The filtrate was concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7g** (0.721 g, 3.00 mmol, 73% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2960, 1126, 1059, 989; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, s), 7.25 (1H, s), 4.72 (1H, t, *J* 5.5), 4.13 (2H, d, *J* 5.5), 3.72-3.65 (2H, m), 3.40-3.33 (2H, m), 1.25 (9H, s), 1.14 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 136.9, 133.1, 126.8, 101.8, 63.8, 55.1, 31.8, 29.3, 15.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{24}N_2O_2$ 240.1838; Found 240.1828.

Ethyl 1-(2,2-diethoxyethyl)-1*H*-pyrazole-3-carboxylate (7h). Ethyl 1*H*-pyrazole-3-carboxylate (1.00 g, 7.17 mmol) was subjected to General Procedure 1. The resultant residue (3:1 r.r. as determined by ^{1}H NMR analysis on the crude material) was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7h** (1.11 g, 4.33 mmol, 60% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2978, 1715, 1229, 1119, 1055, 1024; δ_H (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* 2.0), 6.79 (1H, d, *J* 2.2), 4.79 (1H, t, *J* 5.4), 4.41 (2H, q, *J* 7.0), 4.28 (2H, d, *J* 5.5), 3.74-3.67 (2H, m), 3.46-3.38 (2H, m), 1.40 (3H, t, *J* 7.1), 1.15 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 162.3, 143.9, 132.1, 108.7, 101.3, 64.0, 60.9, 55.7, 15.2, 14.4; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{20}N_2O_4$ 256.1423; Found 256.1416.

4-Bromo-1-(2,2-diethoxyethyl)-3-isopropyl-1*H*-pyrazole (7i). 4-Bromo-3-isopropyl-1*H*-pyrazole (0.409 g, 2.16 mmol) was subjected to General Procedure 1. The resultant residue (7:1 r.r. as determined by ^{1}H NMR analysis on the crude material) was purified by flash column chromatography (SiO_2, eluting with 0-30% methyl *tert*-butyl ether/heptane) to give pyrazole **7i** (0.492 g, 1.61 mmol, 74% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2970, 1125, 1059, 1028; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, s), 4.72 (1H, t, *J* 5.6), 4.11 (2H, d, *J* 5.5), 3.73-3.66 (2H, m), 3.46-3.38 (2H, m), 3.03 (1H, septet, *J* 6.8), 1.28 (6H, d, *J* 6.8), 1.15 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 155.7, 131.1, 101.2, 91.7, 63.7, 55.3, 26.7, 21.6, 15.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{21}BrN_2O_2$ 304.0786; Found 304.0775.

4-Bromo-1-(2,2-diethoxyethyl)-3-(trifluoromethyl)-1*H*-pyrazole (7j). 4-Bromo-3-(trifluoromethyl)-1*H*-pyrazole (0.505 g, 2.35 mmol) was subjected to General Procedure 1. The resultant residue (>19:1 r.r. as determined by ^{1}H NMR analysis on the crude material) was purified by flash column chromatography (SiO_2, eluting with 0-20% methyl *tert*-butyl ether/heptane) to give pyrazole **7j** (0.644 g, 1.95 mmol, 82% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2980, 1231, 1123, 1059, 1003; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s), 4.73 (1H, t, *J* 5.4), 4.21 (2H, d, *J* 5.3), 3.77-3.69 (2H, m), 3.51-3.44 (2H, m), 1.18 (6H, t, *J* 6.9); δ_C (125 MHz, $CDCl_3$) 140.4 (q, *J* 37.2), 133.4, 120.6 (q, *J* 268.9), 100.7, 91.3, 64.0, 56.0, 15.2; δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −62.0; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{14}BrF_3N_2O_2$ 330.0191; Found 330.0175.

1-(2,2-Dimethoxypropyl)-4-iodo-1*H*-pyrazole (7k). To a stirred solution of 4-iodo-1*H*-pyrazole (0.513 g, 2.65 mmol) in dimethyl sulfoxide (4.11 mL) at room temperature was added cesium carbonate (1.30 g, 3.97 mmol) in one portion, followed by a solution of 1-bromo-2,2-dimethoxypropane (0.376 mL, 2.78 mmol) in dimethyl sulfoxide (1.03 mL) dropwise. The reaction mixture was stirred in a 120 °C heating block for 16 hours, then was cooled to room temperature and filtered through celite, washing with ethyl acetate (80 mL). The filtrate was concentrated, then was diluted with water (30 mL), sat. aq. sodium chloride solution (10 mL) and methyl *tert*-butyl ether (30 mL) and the layers were separated. The aqueous layer was extracted with methyl *tert*-butyl ether (50 mL), then the combined organics were dried over Na_2SO_4 and concentrated to give a residue, which was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **7k** (0.645 g, 2.18 mmol, 82% yield) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2957, 1175, 1043, 986, 941; δ_H (400 MHz, $CDCl_3$) 7.50 (1H,s), 7.49 (1H, s), 4.24 (2H, s), 3.29 (6H, s), 1.16 (3H, s); δ_C (100 MHz, $CDCl_3$) 144.0, 134.5, 100.0, 56.6, 56.5, 48.7, 19.7; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_8H_{13}IN_2O_2$ 296.0022; Found 296.0024.

1-(1,1-Diethoxypropan-2-yl)-4-iodo-1*H*-pyrazole (7l). To a stirred solution of 4-iodo-1*H*-pyrazole (0.545 g, 2.81 mmol) in dimethyl sulfoxide (4.36 mL) at room temperature was added cesium carbonate (5.52 g, 16.9 mmol) in one portion, followed by a solution of 2-bromo-1,1-diethoxy-propane (0.991 mL, 5.62 mmol) in dimethyl sulfoxide (1.09 mL) dropwise. The reaction mixture was stirred in a 120 °C heating block for 16 hours, then was cooled to room temperature and filtered through celite, washing with ethyl acetate (100 mL). The filtrate was concentrated then was diluted with water (30 mL), sat. aq. sodium chloride solution (10 mL) and methyl *tert*-butyl ether (30 mL) and the layers were separated. The aqueous layer was extracted with methyl *tert*-butyl ether (30 mL), then the combined organics were dried over Na_2SO_4 and concentrated to give a residue, which was purified by flash column chromatography (SiO_2, eluting with 10-15% ethyl acetate/heptane) to give pyrazole **7l** (0.631 g, 1.95 mmol, 69% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2976, 1115, 1105, 1059, 939; δ_H (400 MHz, $CDCl_3$) 7.52 (1H, s), 7.51 (1H, s), 4.56 (1H, d, *J* 4.5), 4.35 (1H, quint, *J* 6.6), 3.74-3.66 (1H, m), 3.65-3.57 (1H, m), 3.44-3.37 (1H, m), 3.32-3.24 (1H, m), 1.54 (3H, d, *J* 7.2), 1.17 (3H, t, *J* 7.0), 1.08 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 143.9, 133.6, 104.2, 64.5, 64.2, 60.9, 55.3,

15.2, 15.1, 14.7; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{17}IN_2O_2$ 324.0335; Found 324.0328.

General Procedure 2 for formylation of pyrazole derivatives. To a flask was added tetrahydrofuran (6 mL/g) and diisopropylamine (1.6 equiv.) at room temperature and the mixture was stirred in a dry-ice/acetone bath. To the mixture was added *n*-butyl lithium solution (2.5 M in hexanes, 1.5 equiv.) dropwise and the mixture was stirred in a dry-ice/acetone bath for 30 minutes. To the reaction mixture was added a solution of the pyrazole **7** (1 equiv.) in tetrahydrofuran (2 mL/g) dropwise and the mixture was stirred in a dry-ice/acetone bath for 30 minutes. To the reaction mixture was added a solution of *N*,*N*-dimethylformamide (1.8 equiv.) in tetrahydrofuran (2 mL/g) dropwise and the reaction mixture was stirred in a dry-ice/acetone bath for 1 hour. To the reaction mixture was added 2-propanol (2.5 equiv.) dropwise and the reaction mixture was transferred to an ice/water bath. To the reaction mixture was added sat. aq. ammonium chloride solution (20 mL/g) over 5 minutes and water (5 mL/g). The mixture was extracted with methyl *tert*-butyl ether (2 x 50 mL/g) and the combined organics were dried over sodium sulfate and concentrated to give a residue which was purified as specified.

1-(2,2-Diethoxyethyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (8a). Pyrazole **7a** (0.516 g, 1.66 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8a** (0.427 g, 1.26 mmol, 75% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2974, 1684, 1125, 1057, 982; δ_H (400 MHz, $CDCl_3$) 9.81 (1H, s), 7.61 (1H, s), 4.81 (1H, t, *J* 5.7), 4.68 (2H, d, *J* 5.7), 3.74-3.66 (2H, m), 3.51-3.43 (2H, m), 1.13 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 180.6, 144.8, 136.3, 100.3, 68.7, 62.7, 53.7, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{15}IN_2O_3$ 338.0127; Found 338.0118.

4-Bromo-1-(2,2-diethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (8b). Pyrazole **7b** (1.59 g, 6.07 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8b** (1.53 g, 5.27 mmol, 86% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2976, 1686, 1126, 1059, 976; δ_H (400 MHz, $CDCl_3$) 9.90 (1H, s), 7.56 (1H, s), 4.82 (1H, t, *J* 5.6), 4.65 (2H, d, *J* 5.5), 3.74-3.66 (2H, m), 3.52-3.44 (2H, m), 1.14 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 179.3, 139.9, 134.9, 103.6, 100.3, 62.6, 53.9, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{15}BrN_2O_3$ 290.0266; Found 290.0256.

1-(2,2-Diethoxyethyl)-4-fluoro-1*H*-pyrazole-5-carbaldehyde (8c). Pyrazole **7c** (1.61 g, 7.98 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8c** (1.63 g, 7.11 mmol, 89% yield) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2978, 1690, 1126, 1063; δ_H (400 MHz, $CDCl_3$) 9.89 (1H, s), 7.41 (1H, d, *J* 3.9), 4.80 (1H, t, *J* 5.6), 4.56 (2H, d, *J* 5.7), 3.74-3.66 (2H, m), 3.51-3.44 (2H, m), 1.14 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$); 177.0 (d, *J* 2.9), 153.9 (d, *J* 266.3), 125.7 (d, *J* 11.7), 125.6 (d, *J* 16.9), 100.3, 62.7, 54.4, 15.1; δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −167.7; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{15}FN_2O_3$ 230.1067; Found 230.1062.

1-(2,2-Diethoxyethyl)-4-(trifluoromethyl)-1*H*-pyrazole-5-carbaldehyde (8d). Pyrazole **7d** (0.898 g, 3.56 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8d** (0.779 g, 2.78 mmol, 78% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2980, 1703, 1254, 1215, 1126, 1069; δ_H (400 MHz, $CDCl_3$) 10.05 (1H, s), 7.79 (1H, s), 4.83 (1H, t, *J* 5.6), 4.71 (2H, d, *J* 5.7), 3.75-3.68 (2H, m), 3.51-3.43 (2H, m), 1.13 (6H, t, *J* 7.1); δ_C (125MHz, $CDCl_3$) 178.7, 137.2 (q, *J* 3.6), 136.3 (q, *J* 3.6), 122.0 (q, *J* 268.0), 118.3 (q, *J* 39.1), 100.3, 63.0, 54.1, 15.1; δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −54.5; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{15}F_3N_2O_3$ 280.1035; Found 280.1063.

Ethyl 1-(2,2-diethoxyethyl)-5-formyl-1*H*-pyrazole-4-carboxylate (8e). Pyrazole **7e** (1.83 g, 7.13 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8e** (1.52 g, 5.55 mmol, 77% yield corrected for 4:1 mixture of **8e**:**10**) as a pale yellow oil. Data listed for major product. ν_{max} (thin film)/cm^{-1} 2978, 1717, 1688, 1209, 1049; δ_H (400 MHz, $CDCl_3$) 10.50 (1H, s), 7.95 (1H, s), 4.85 (1H, t, *J* 4.3), 4.72 (2H, d, *J* 4.3), 4.37 (2H, q, *J* 7.2), 3.73-3.66 (2H, m), 3.51-3.44 (2H, m), 1.39 (3H, t, *J* 6.9), 1.13 (6H, t, *J* 6.6); δ_C (100 MHz, $CDCl_3$) 182.4, 162.2, 140.9, 138.7, 119.2, 100.3, 62.5, 61.1, 54.0, 15.1, 14.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{20}N_2O_5$ 284.1372; Found 284.1365.

1-(2,2-Diethoxyethyl)-5-formyl-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide (8f). To a flask was added tetrahydrofuran (2.45 mL) and diisopropylamine (0.472 mL, 3.36 mmol) at room temperature and the mixture was stirred in a dry-ice/acetone bath. To the mixture was added *n*-butyl lithium solution (2.5 M in hexanes, 1.28 mL, 3.20 mmol) dropwise and the mixture was stirred in a dry-ice/acetone bath for 30 minutes. To the reaction mixture was added a solution of pyrazole **7f** (408 mg, 1.60 mmol) in tetrahydrofuran (0.816 mL) dropwise and the mixture was stirred in a dry-ice/acetone bath for 30 minutes. To the reaction mixture was added a solution of *N*,*N*-dimethylformamide (0.223 mL, 2.88 mmol) in tetrahydrofuran (0.816 mL) dropwise and the reaction mixture was stirred in a dry-ice/acetone bath for 1 hour. To the reaction mixture was added 2-propanol (0.305 mL, 4.00 mmol) dropwise and the reaction mixture was transferred to an ice/water bath. To the reaction mixture was added sat. aq. ammonium chloride solution (20 mL) over 5 minutes and water (5 mL). The mixture was extracted with 2-methyltetrahydrofuran (3 x 30 mL) and then with 9:1 ethyl acetate/2-propanol (3 x 30 mL) and the combined organics were dried over sodium sulfate and concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with 50-80% ethyl acetate/heptane) to give pyrazole-aldehyde **8f** (0.356 g, 1.26 mmol, 78% yield) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2976, 1688, 1624, 1396, 1126, 1057; δ_H (400 MHz, $CDCl_3$) 10.09 (1H, s), 7.62 (1H, s), 4.84 (1H, t, *J* 5.5), 4.67 (2H, d, *J* 5.5), 3.75-3.68 (2H, m), 3.52-3.45 (2H, m), 3.12 (6H, s), 1.14 (6H, t, *J* 6.8); δ_C (100 MHz, $CDCl_3$) 181.1, 163.4, 137.8, 137.6, 123.3, 100.4, 62.8, 53.8, 39.2, 35.4, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{21}N_3O_4$ 283.1532; Found 283.1537.

Ethyl 1-(2,2-diethoxyethyl)-5-formyl-1*H*-pyrazole-3-carboxylate (8h). Pyrazole **7h** (1.11 g, 4.33 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8h**

(0.549 g, 1.96 mmol, 45% yield corrected for 13:1 mixture of **8h**:**11**) as a white solid. Data listed for major product. m.p. 39-42 °C; ν_{max} (thin film)/cm^{-1} 2978, 1722, 1692, 1213, 1123, 1057; δ_H (400 MHz, $CDCl_3$) 9.93 (1H, s), 7.41 (1H, s), 4.86 (1H, t, *J* 5.6), 4.74 (2H, d, *J* 5.3), 4.44 (2H, q, *J* 7.1), 3.75-3.68 (2H, m), 3.49-3.41 (2H, m), 1.41 (3H, t, *J* 7.2), 1.12 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 179.5, 161.2, 143.3, 141.0, 115.3, 100.6, 63.2, 61.3, 53.8, 15.0, 14.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{20}N_2O_5$ 284.1372; Found 284.1376.

4-Bromo-1-(2,2-diethoxyethyl)-3-isopropyl-1*H*-pyrazole-5-carbaldehyde (8i). Pyrazole **7i** (0.415 g, 1.36 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazole-aldehyde **8i** (0.212 g, 0.636 mmol, 46% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2972, 1686, 1119, 1061, 1030; δ_H (400 MHz, $CDCl_3$) 9.85 (1H, s), 4.81 (1H, t, *J* 5.6), 4.59 (2H, d, *J* 5.7), 3.74-3.67 (2H, m), 3.49-3.41 (2H, m), 3.07 (1H, septet, *J* 7.0), 1.31 (6H, d, *J* 7.0), 1.12 (6H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 179.7, 155.7, 135.1, 102.4, 100.3, 62.4, 53.5, 26.5, 21.4, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{13}H_{21}BrN_2O_3$ 332.0736; Found 332.0729.

4-Bromo-1-(2,2-diethoxyethyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carbaldehyde (8j). Pyrazole **7j** (0.592 g, 1.79 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8j** (0.491 g, 1.37 mmol, 76% yield) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2980, 1695, 1225, 1130, 1059, 1009; δ_H (400 MHz, $CDCl_3$) 9.92 (1H, s), 4.84 (1H, t, *J* 5.7), 4.69 (2H, d, *J* 5.7), 3.75-3.67 (2H, m), 3.52-3.45 (2H, m), 1.13 (6H, t, *J* 7.0); δ_C (126 MHz, $CDCl_3$) 179.1, 140.3 (q, *J* 37.2), 136.7, 120.0 (q, *J* 269.8), 100.9, 98.8, 62.8, 54.2, 15.0; δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −62.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{14}BrF_3N_2O_3$ 358.0140; Found 358.0120.

1-(2,2-Dimethoxypropyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (8k). Pyrazole **7k** (0.573 g, 1.94 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8k** (0.535 g, 1.65 mmol, 85% yield) as a pale yellow solid. m.p. 76-79 °C; ν_{max} (thin film)/cm^{-1} 2992, 1686, 1045; δ_H (400 MHz, $CDCl_3$) 9.81 (1H, s), 7.63 (1H, s), 4.74 (2H, s), 3.28 (6H, s), 1.17 (3H, s); δ_C (100 MHz, $CDCl_3$) 180.7, 145.0, 136.6, 100.3, 69.1, 54.3, 48.7, 19.9; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{13}IN_2O_3$ 323.9971; Found 323.9964.

1-(1,1-Diethoxypropan-2-yl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (8l). Pyrazole **7l** (0.509 g, 1.57 mmol) was subjected to General Procedure 2. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole-aldehyde **8l** (0.490 g, 1.39 mmol, 88% yield) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2976, 1688, 1113, 1061, 1015, 957; δ_H (400 MHz, $CDCl_3$) 9.82 (1H, s), 7.62 (1H, s), 5.47 (1H, quint, *J* 7.0), 4.69 (1H, d, *J* 7.2), 3.75-3.68 (1H, m), 3.59-3.49 (2H, m), 3.29-3.21 (1H, m), 1.55 (3H, d, *J* 6.8), 1.22 (3H, t, *J* 7.0), 0.94 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 180.8, 144.6, 136.4, 104.2, 68.6, 63.5, 62.7, 57.9, 15.9, 15.2, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{17}IN_2O_3$ 352.0284; Found 352.0274.

General Procedure 3 for deprotection and cyclization of pyrazole derivatives. To a flask was added the pyrazole-5-carbaldehyde **8** (1 equiv.), trifluoroacetic acid (4 mL/g), water (2 mL/g) and 2-methyltetrahydrofuran (2 mL/g) at room temperature. The reaction mixture was stirred in a 40 °C heating block for 3 hours, then was cooled to room temperature and concentrated to give a residue, which was concentrated from toluene (3 x 5 mL/g). The resultant residue was combined with ethanol (8 mL/g), acetic acid (3 equiv.) and ammonium acetate (3 equiv.) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and then water (20 mL/g) and 2-methyltetrahydrofuran (20 mL/g) were added. The mixture was stirred at room temperature and solid potassium carbonate was added portionwise until the aqueous layer reached pH 8, then the layers were separated and the aqueous layer was extracted with 2-methyltetrahydrofuran (20 mL/g). The combined organics were dried over sodium sulfate and concentrated to give a residue which was purified as specified.

3-Iodopyrazolo[1,5-*a*]pyrazine (9a). Pyrazole-aldehyde **8a** (0.337 g, 1.00 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9a** (0.205 g, 0.837 mmol, 83% yield) as a white solid. m.p. 114-116 °C; ν_{max} (thin film)/cm^{-1} 3105, 1506, 1339, 1287, 1227; δ_H (400 MHz, $CDCl_3$) 8.97 (1H, s), 8.36 (1H, d, *J* 4.9), 8.05 (1H, s), 7.93 (1H, d, *J* 4.9); δ_C (100 MHz, $CDCl_3$) 146.7, 144.6, 136.1, 130.0, 121.9, 50.0; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_6H_4IN_3$ 244.9450; Found 244.9448.

3-Bromopyrazolo[1,5-*a*]pyrazine (9b). *Method A*: Pyrazole-aldehyde **8b** (0.538 g, 1.85 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9b** (0.301 g, 1.52 mmol, 82% yield) as a pale yellow solid. *Method B*: 4-Bromo-1*H*-pyrazole (3.08 g, 21.0 mmol) was subjected to General Procedure 1. The resultant residue was taken forward without any further purification and subjected to General Procedure 2, assuming 100% yield for the first step. The resultant residue was taken forward without any further purification and subjected to General Procedure 3, assuming 100% yield for the second step. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9b** (2.65 g, 13.4 mmol, 63% overall yield from 4-bromo-1*H*-pyrazole) as a pale yellow solid. m.p. 103-106 °C; ν_{max} (thin film)/cm^{-1} 3015, 1514, 1425, 1346, 1310, 1294, 1269, 1225; δ_H (400 MHz, $CDCl_3$) 9.04 (1H, s), 8.34 (1H, d, *J* 4.9), 8.01 (1H, s), 7.93 (1H, d, *J* 5.1); δ_H (400 MHz, $(CD_3)_2SO$) 9.13 (1H, s), 8.85 (1H, d, *J* 4.5), 8.36 (1H, s), 8.02 (1H, d, *J* 4.5); δ_C (100 MHz, $CDCl_3$) 143.6, 142.1, 133.6, 129.9, 121.8, 86.5; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_6H_4BrN_3$ 196.9589; Found 196.9578. Data were consistent with those previously reported in the literature.[20]

3-Fluoropyrazolo[1,5-*a*]pyrazine (9c). Pyrazole-aldehyde **8c** (1.44 g, 6.24 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9c** (0.574 g, 4.18 mmol, 67% yield) as a white solid. m.p. 65-68 °C; ν_{max} (thin film)/cm^{-1} 3101, 1622, 1558, 1481, 1362, 1105; δ_H (400 MHz, $CDCl_3$) 9.07 (1H, s), 8.21 (1H, d, *J* 3.9), 7.87 (1H, d, *J* 3.5), 7.83 (1H, d, *J* 4.9); δ_C (100 MHz, $CDCl_3$) 142.3 (d, *J* 5.9), 141.2 (d, *J* 251.6), 129.2, 127.6 (d, *J* 11.7), 123.2 (d, *J* 27.9), 121.3; δ_F

(^{1}H decoupled, 376 MHz, $CDCl_3$) −178.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_6H_4FN_3$ 137.0389; Found 137.0391.

3-(Trifluoromethyl)pyrazolo[1,5-*a*]pyrazine(9d). Pyrazole-aldehyde **8d** (0.637 g, 2.27 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9d** (0.294 g, 1.57 mmol, 69% yield) as a white solid. m.p. 68-71 °C; ν_{max} (thin film)/cm^{-1} 3134, 1545, 1362, 1217, 1117, 1007; δ_H (400 MHz, $CDCl_3$) 9.25 (1H, s), 8.46 (1H, d, *J* 4.7), 8.26 (1H, s), 8.09 (1H, d, *J* 4.3); δ_C (125 MHz, $CDCl_3$) 143.6, 140.3 (q, *J* 3.0), 132.9, 131.0, 122.5 (q, *J* 268.0), 121.9, 104.6 (q, *J* 40.9); δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −55.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_4F_3N_3$ 187.0357; Found 187.0355.

Ethyl pyrazolo[1,5-*a*]pyrazine-3-carboxylate (9e). Pyrazole-aldeyhde **8e** (1.42 g, 5.19 mmol corrected for 4:1 mixture of **8e**:**10**) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9e** (0.919 g, 4.81 mmol, 92% yield) as a yellow solid. m.p. 85-87 °C; ν_{max} (thin film)/cm^{-1} 3100, 1697, 1487, 1352, 1285, 1233, 1057, 743; δ_H (400 MHz, $CDCl_3$) 9.61 (1H, s), 8.48 (1H, s), 8.45 (1H, dd, *J* 4.7, 1.4), 8.09 (1H, d, *J* 4.5), 4.44 (2H, q, *J* 7.0), 1.45 (3H, t, *J* 7.1); δ_H (400 MHz, $(CD_3)_2SO$) 9.49 (1H, s), 8.99 (1H, d, *J* 4.9), 8.62 (1H, s), 8.20 (1H, d, *J* 4.7), 4.37 (2H, q, *J* 7.1), 1.37 (3H, t, *J* 7.2); δ_C (100 MHz, $CDCl_3$) 162.3, 145.6, 144.7, 135.1, 131.3, 122.1, 106.2, 60.7, 14.4; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_9N_3O_2$ 191.0695; Found 191.0695. Data were consistent with those previously reported in the literature.[20]

***N*,*N*-Dimethylpyrazolo[1,5-*a*]pyrazine-3-carboxamide (9f).** Pyrazole-aldeyhde **8f** (0.365 g, 1.29 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-10% methanol/ethyl acetate) to give pyrazolo[1,5-*a*]pyrazine **9f** (0.244 g, 1.28 mmol, 99% yield) as a white solid. m.p. 123-126 °C; ν_{max} (thin film)/cm^{-1} 3115, 1628, 1611, 1526, 1410, 1042; δ_H (400 MHz, $CDCl_3$) 9.55 (1H, s), 8.40 (1H, d, *J* 4.5), 8.18 (1H, s), 8.03 (1H, d, *J* 4.7), 3.26 (6H, br. s); δ_C (100 MHz, $CDCl_3$) 163.6, 146.3, 141.4, 136.0, 130.9, 121.5, 108.9, 39.0, 35.9; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{10}N_4O$ 190.0855; Found 190.0871.

Ethyl pyrazolo[1,5-*a*]pyrazine-2-carboxylate (9h). Pyrazole-aldeyhde **8h** (0.449 g, 1.60 mmol corrected for 13:1 mixture of **8h**:**11**) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9h** (0.240 g, 1.25 mmol, 78% yield) as an off-white solid. m.p. 111-113 °C; ν_{max} (thin film)/cm^{-1} 3105, 1209, 1105, 1016; δ_H (400 MHz, $CDCl_3$) 9.15 (1H, s), 8.45 (1H, d, *J* 4.5), 8.00 (1H, d, *J* 4.7), 7.36 (1H, s), 4.51 (2H, q, *J* 7.1), 1.46 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 161.9, 146.0, 145.3, 136.2, 131.2, 121.9, 102.0, 61.7, 14.3; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_9N_3O_2$ 191.0695; Found 191.0695.

3-Bromo-2-isopropylpyrazolo[1,5-*a*]pyrazine (9i). Pyrazole-aldeyhde **8i** (0.168 g, 0.503 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9i** (0.102 g, 0.423 mmol, 84% yield) as a yellow solid. m.p. 45-49 °C; ν_{max} (thin film)/cm^{-1} 2968, 1512, 1489, 1314, 1271; δ_H (400 MHz, $CDCl_3$) 8.93 (1H, s), 8.27 (1H, d, *J* 4.3), 7.85 (1H, d, *J* 4.7), 3.32 (1H, septet, *J* 7.0), 1.40 (6H, d, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 159.0, 143.0, 134.2, 129.3, 121.6, 84.8, 27.0, 21.6; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{10}BrN_3$ 239.0058; Found 239.0048.

3-Bromo-2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrazine (9j). Pyrazole-aldeyhde **8j** (0.427 g, 1.19 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9j** (0.279 g, 1.05 mmol, 88% yield) as an off-white solid. m.p. 72-75 °C; ν_{max} (thin film)/cm^{-1} 3094, 1207, 1182, 1136, 1024; δ_H (400 MHz, $CDCl_3$) 9.14 (1H, s), 8.38 (1H, dd, *J* 4.9, 1.4), 8.10 (1H, d, *J* 4.9); δ_C (125 MHz, $CDCl_3$) 144.7, 142.2 (q, *J* 37.2), 134.9, 132.0, 121.7, 120.4 (q, *J* 270.7), 85.0; δ_F (^{1}H decoupled, 376 MHz, $CDCl_3$) −61.5; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_3BrF_3N_3$ 264.9462; Found 264.9455.

3-Iodo-6-methylpyrazolo[1,5-*a*]pyrazine (9k). Pyrazole-aldehyde **8k** (0.482 g, 1.49 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9k** (0.345 g, 1.33 mmol, 89% yield) as an off-white solid. m.p. 117-120 °C; ν_{max} (thin film)/cm^{-1} 3103, 1520, 1420, 1321, 1277; δ_H (400 MHz, $CDCl_3$) 8.87 (1H, s), 8.19 (1H, s), 7.97 (1H, s), 2.57 (3H, s); δ_C (100 MHz, $CDCl_3$) 146.2, 143.4, 139.2, 134.7, 119.0, 49.2, 20.7; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_6IN_3$ 258.9606; Found 258.9604.

3-Iodo-7-methylpyrazolo[1,5-*a*]pyrazine (9l). Pyrazole-aldehyde **8l** (0.423 g, 1.20 mmol) was subjected to General Procedure 3. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **9l** (0.259 g, 1.00 mmol, 83% yield) as a white solid. m.p. 107-110 °C; ν_{max} (thin film)/cm^{-1} 3084, 1526, 1321, 1300, 1092; δ_H (400 MHz, $CDCl_3$) 8.88 (1H, s), 8.08 (1H, s), 7.81 (1H, s), 2.74 (3H, s); δ_C (100 MHz, $CDCl_3$) 146.3, 142.2, 136.0, 131.9, 128.9, 50.0, 14.2; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_6IN_3$ 258.9606; Found 258.9605.

(±)-1-(1-(2,2-Diethoxyethyl)-4-iodo-1*H*-pyrazol-5-yl)ethan-1-ol (16). To a flask was added pyrazole-aldehyde **8a** (0.612 g, 1.81 mmol) and tetrahydrofuran (6.12 mL) at room temperature and the mixture was stirred in a dry-ice/acetone bath. To the reaction mixture was added methylmagnesium bromide solution (3.0 M in diethyl ether, 1.81 mL, 5.43 mmol) dropwise and the mixture was stirred in a dry-ice/acetone bath for 1 hour. The reaction mixture was transferred to a −50 °C cooling bath and stirred for 30 minutes, then 2-propanol (0.346 mL, 4.52 mmol) was added dropwise and the reaction mixture was transferred to an ice/water bath. To the reaction mixture was added sat. aq. ammonium chloride solution (20 mL) over 5 minutes and water (5 mL). The mixture was extracted with methyl *tert*-butyl ether (2 x 30 mL) and the combined organics were dried over sodium sulfate and concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazole **16** (0.494 g, 1.40 mmol, 77% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3356, 2976, 1373, 1115, 1061; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, s), 5.18-5.10 (1H, m), 4.79 (1H, t, *J* 5.2), 4.60 (1H, dd, *J* 14.0, 7.0), 4.35 (1H, dd, *J* 13.7, 4.1), 3.78-3.67 (2H, m), 3.59-3.49 (2H, m), 3.36-3.28 (1H, m), 1.54 (3H, d, *J* 6.4), 1.19 (3H, t, *J* 6.9), 1.08 (3H, t, *J* 6.9); δ_C

(100 MHz, $CDCl_3$) 145.5, 144.5, 101.8, 65.0, 63.7, 63.6, 56.9, 53.3, 22.8, 15.2, 15.0; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{19}IN_2O_3$ 354.0440; Found 354.0434.

1-(1-(2,2-Diethoxyethyl)-4-iodo-1*H*-pyrazol-5-yl)ethan-1-one (13). To a flask was added pyrazole **16** (0.417 g, 1.18 mmol) and dichloromethane (4.17 mL) at room temperature and the mixture was stirred in an ice/water bath. To the mixture was added iodobenzene diacetate (773 mg, 2.35 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.0184 g, 0.118 mmol) and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added sat. aq. sodium thiosulfate solution (5mL) and the mixture was stirred at room temperature for 30 minutes, then water (10 mL) was added. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organics were dried over sodium sulfate and concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with 0-20% ethyl acetate/heptane) to give pyrazole **13** (0.377 g, 1.07 mmol, 91% yield) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2976, 1678, 1244, 1125, 1061; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s), 4.74 (1H, t, *J* 5.3), 4.64 (2H, d, *J* 5.3), 3.71-3.64 (2H, m), 3.49-3.41 (2H, m), 2.76 (3H, s), 1.13 (6H, t, *J* 7.1); δ_C (100 MHz, $CDCl_3$) 190.4, 145.5, 141.1, 100.7, 62.7, 62.7, 54.5, 31.6, 15.1; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{17}IN_2O_3$ 352.0284; Found 352.0284.

3-Iodo-4-methylpyrazolo[1,5-*a*]pyrazine (14). To a flask was added pyrazole **13** (329 mg, 0.934 mmol), trifluoroacetic acid (1.32 mL), water (0.658 mL) and 2-methyltetrahydrofuran (0.658 mL) at room temperature. The reaction mixture was stirred in a 40 °C heating block for 3 hours, then was cooled to room temperature and concentrated to give a residue, which was concentrated from toluene (3 x 5 mL). The resultant residue was combined with ethanol (2.08 mL), acetic acid (0.164 mL, 2.80 mmol) and ammonium acetate (0.216 g, 2.80 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and then water (20 mL) and 2-methyltetrahydrofuran (20 mL) were added. The mixture was stirred at room temperature and solid potassium carbonate was added portionwise until the aqueous layer reached pH 8. The layers were then separated and the aqueous layer was extracted with 2-methyltetrahydrofuran (20 mL). The combined organics were dried over sodium sulfate, and concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give pyrazolo[1,5-*a*]pyrazine **14** (0.195 g, 0.754 mmol, 80% yield) as a yellow solid. m.p. 137-139 °C; ν_{max} (thin film)/cm^{-1} 3082, 1487, 1377, 1325; δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 4.7), 8.00 (1H, s), 7.73 (1H, d, *J* 4.7), 3.07 (3H, s); δ_C (100 MHz, $CDCl_3$) 154.0, 147.8, 134.6, 128.9, 121.2, 49.1, 23.6; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_7H_6IN_3$ 258.9606; Found 258.9601.

General Procedure 4 for deprotection and reductive amination of pyrazole derivatives. To a flask was added the pyrazole-aldehyde **8a** (1 equiv.), trifluoroacetic acid (4 mL/g), water (2 mL/g) and 2-methyltetrahydrofuran (2 mL/g) at room temperature. The reaction mixture was stirred in a 40 °C heating block for 3 hours, then was cooled to room temperature and concentrated to give a residue, which was concentrated from toluene (3 x 5 mL/g). The resultant residue was combined with ethyl acetate (13 mL/g) at room temperature. The mixture was stirred in an ice/water bath and a solution of amine (1.2 equiv.) in ethyl acetate (12 mL/g) was added, followed by sodium triacetoxyborohydride (3.0 equiv.). The mixture was stirred at room temperature for 2 hours, then was transferred to an ice/water bath and sat. aq. sodium bicarbonate solution (20 mL/g) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (20 mL/g). The combined organics were dried over sodium sulfate and concentrated to give a residue which was purified as specified.

3-Iodo-5-(4-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (15a). Pyrazole-aldehyde **8a** (0.507 g, 1.50 mmol) was subjected to General Procedure 4. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give tetrahydropyrazolo[1,5-*a*]pyrazine **15a** (0.264 g, 0.715 mmol, 47% yield) as a red solid. m.p. 90-95 °C; ν_{max} (thin film)/cm^{-1} 2930, 1510, 1348, 1244, 1173, 1032; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s), 7.27 (2H, d, *J* 8.5), 6.89 (2H, d, *J* 8.4), 4.15 (2H, t, *J* 5.3), 3.82 (3H, s), 3.69 (2H, s), 3.57 (2H, s), 2.88 (2H, t, *J* 5.3); δ_C (100 MHz, $CDCl_3$) 159.1, 143.4, 138.8, 130.1, 129.1, 113.9, 61.1, 55.3, 53.6, 50.3, 49.3, 47.8; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{16}IN_3O$ 369.0338; Found 369.0334.

5-(*tert*-Butyl)-3-iodo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (15b). Pyrazole-aldehyde **8a** (0.510 g, 1.51 mmol) was subjected to General Procedure 4. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give tetrahydropyrazolo[1,5-*a*]pyrazine **15b** (0.350 g, 1.15 mmol, 75% yield) as a yellow solid. m.p. 66-70 °C; ν_{max} (thin film)/cm^{-1} 2968, 1350, 1204, 1179, 933; δ_H (400 MHz, $CDCl_3$) 7.46 (1H, s), 4.15 (2H, t, *J* 5.2), 3.68 (2H, s), 2.96 (2H, t, *J* 5.2), 1.19 (9H, s); δ_C (100 MHz, $CDCl_3$) 143.3, 139.4, 54.2, 53.7, 49.0, 43.9, 43.8, 25.9; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{16}IN_3$ 305.0389; Found 305.0387.

5-Cyclopropyl-3-iodo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (15c). Pyrazole-aldehyde **8a** (0.506 g, 1.50 mmol) was subjected to General Procedure 4. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate/heptane) to give tetrahydropyrazolo[1,5-*a*]pyrazine **15c** (0.234 g, 0.808 mmol, 53% yield) as a pink oil. ν_{max} (thin film)/cm^{-1} 2926, 1346, 1229, 970;δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s), 4.16 (2H, t, *J* 5.5), 3.71 (2H, s), 3.10 (2H, t, *J* 5.5), 1.95-1.90 (1H, m), 0.62-0.58 (2H, m), 0.55-0.52 (2H, m); δ_C (100 MHz, $CDCl_3$) 143.3, 138.7, 53.5, 50.3, 50.2, 47.7, 37.5, 6.5; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_9H_{12}IN_3$ 289.0076; Found 289.0071.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

*Email: lindsay-scott_peter@lilly.com

Notes

The authors declare no competing financial interest.

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