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Regioselective coupling reactions of 2,4-diaminopyridine derivatives with aryl halides: the synthesis of elaborated pyridines

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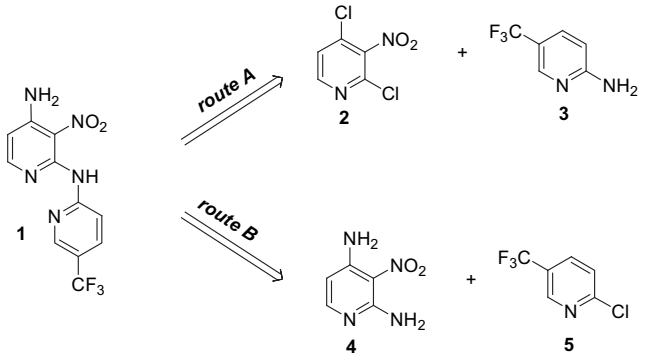
ABSTRACT

The development of a synthetically useful, regioselective cross-coupling of 2,4-diaminopyridines with aryl and heteroaryl halides is reported. Selectivity for coupling through either amine is controlled by a simple change in the reaction conditions. Cross-coupling through the 2-amino group predominates in the presence of a palladium catalyst, whilst the 4-amino coupled product predominates in the absence of palladium.

1. Introduction

The prevalence of nitrogen containing small molecules among the ranks of biologically active molecules is well known.[1] As a result, the development of selective carbon–nitrogen bond forming reactions has been the focus of a number of research groups.[2] Specifically, palladium mediated cross-coupling of amines or amides with aryl or heteroaryl halides is well studied and widely used.[3] Relevant to the study discussed herein, the regioselective coupling of polyhalogenated pyridines with amines has been reported.[4] We now wish to report an orthogonal reaction in which 2,4-diaminopyridines are regioselectively coupled to aryl and heteroaryl halides through either the 2- or 4-amino group, depending on the reaction conditions (Scheme 1).



Scheme 1.

During the course of a recent project we required an efficient, scalable synthetic route to compound **1**. We anticipated **1** could be accessed through one of two preferred routes. There was literature precedent, which suggested that a regioselective reaction of 2,4-dichloropyridine **2** with **3** (route **A**) may afford our desired target.[5] Whilst an alternative construction resulting from selective coupling of 2,4-diaminopyridine **4** with **5** (route **B**) was unprecedented; however, the possibility of employing readily accessed **4** as an intermediate to **1**, was too attractive to ignore.

In this account we report the successful realisation of a regioselective arylation of 2,4-diaminopyridines. This methodology enables the efficient synthesis of two regioisomeric compounds from a common intermediate, greatly simplifying such syntheses.

2. Results and discussion

2.1. Regioselective amination of 2,4-diamino-3-nitropyridine

We initially investigated the selective reaction of 2,4-dichloro-3-nitropyridine **2** (route A),[6] as selective amination reactions at either the 2- or 4-positions have been previously reported. Of particular interest was the reaction of 2,4-dichloro-3-nitropyridines with primary amines, which generally display modest to good selectivity for substitution of the 4-chloride.[7] Meanwhile palladium-catalysed coupling reactions with benzophenone imine have been shown to be selective towards the 2-isomer.[8] Unfortunately, in our case the yields observed in both types of reaction were generally modest, with competing chloride hydrolysis being a significant problem. This prompted us to pursue the alternative synthesis from 2,4-diamino-3-nitropyridine **4** (route B), which

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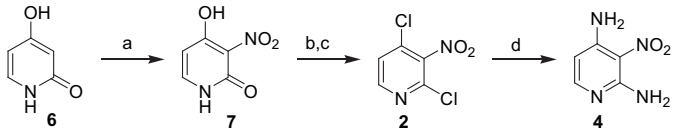
could be easily obtained by complete amination of **2** upon treatment with ammonia at elevated temperatures and pressures (Scheme 2).[9]

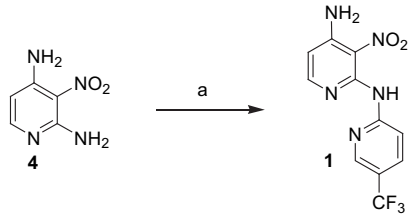


Scheme 2. a) HNO_3, H_2SO_4, 0 °C, 98%; b) oxalyl chloride, DMF, MeCN, 91%; c) $POCl_3$, LiCl, 37% HCl, 105 °C then MeCN for work up 89%; d) NH_3, H_2O, 91 °C, 4.09 bar, 94%.

2.2. Selective 2-arylation

Cognisant of the extensive literature on palladium-catalysed amination reactions, we were now in a position to screen our desired reaction (Table 1, Scheme 3). A range of typical palladium–ligand combinations were tested along with a screen of bases. We were pleased to see that the palladium–Xantphos derived catalyst was highly selective for the 2-arylation of pyridine **4** (Table 1, entry 2), without the need for protecting groups. Optimisation of this reaction was performed employing 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as a solvent. Potassium *tert*-butoxide (*t*-BuOK) was found to be the base of choice, giving rise to the best regioisomeric ratio (Table 1, entries 11 and 12). It is noteworthy that a bidentate ligand must be employed in order for the catalytic cycle to predominate over the background reaction to generate the 4-arylated products (Table 1, entries 5 and 6). Using $Pd(dba)_2$ as the catalyst was favoured over $Pd_2(dba)_3$, as the amount of 2,4-bisarylated by-product obtained was lower and hence the overall yield of the 2-aryl product could be maximised. The optimised conditions for the palladium cross-coupling of 2,4-diamino-3-nitropyridine **4** and 2-chloro-5-trifluoromethylpyridine **5** are highlighted below (Table 1, entry 11). These optimal conditions were shown to afford the highest *N*-2 versus *N*-4 selectivity (22:1) whilst minimising the formation of the 2,4-bis product.

The regioselectivity of the palladium-catalysed amination can be rationalised on the ability of the pyridine nitrogen to form complexes with metals.[10] Two regioisomeric intermediates can be proposed for the formation of 2-arylaminopyridine and its 4-isomer (Fig. 1). Intermediate **A**, leading to the major reaction product, is stabilised by coordination of the pyridine nitrogen to the metallic centre, whereas no such stabilisation is possible for intermediate **B**.



Scheme 3. a) 2-Chloro-5-trifluoromethylpyidine **5**, 5 mol% $Pd(dba)_2$, 5 mol% Xantphos, 2.2 equiv *t*-BuOK (1 M in THF), DMPU, 80 °C.

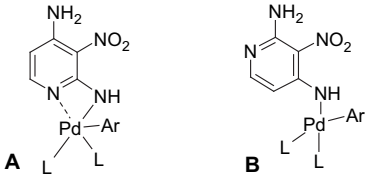


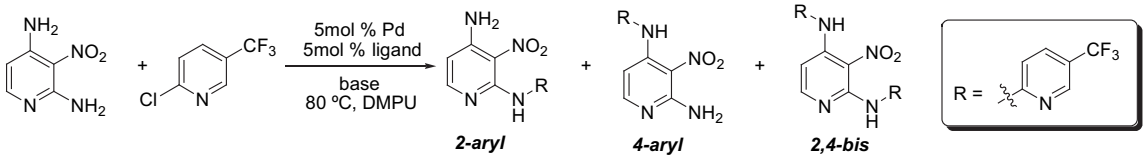
Figure 1.

These optimised conditions were applied to a range of substrates to produce the corresponding 2-substituted heterocycles in good to excellent yields, with selectivities for the 2- versus 4-mono-arylation ranging from 9 to 1 to complete selectivity in the cases of 4-nitrobenzylbromide (Table 2, entry 3). Another parameter of importance was the rate of addition of base to the reaction mixture. It was found that simply charging the base in one portion at the beginning of the reaction led to formation of large amount of the 2,4-bis-arylated product. The formation of this side product could be minimised by addition of the base over 2 h. This dimeric impurity could be easily rejected by chromatography.

2.3. Selective 4-arylation

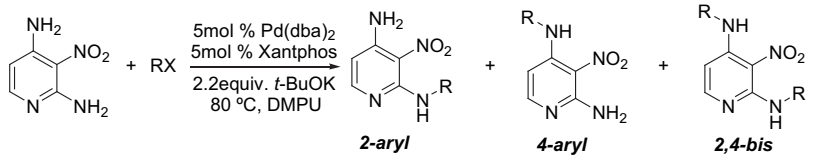
During the screen of palladium catalysts and ligands we noticed that in the absence of a bidentate ligand the undesired 4-arylated product **8** predominated in the reaction mixture (Table 1, entry 5; Scheme 4) and this selectivity was further enhanced when no ligand was present (Table 1, entry 6). This led us to study this process as a potential extension of this methodology, whereby either the 2- or 4-arylated products could be afforded directly from the same

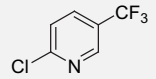
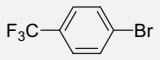
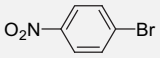
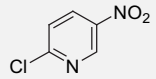
Table 1
Optimisation of the palladium-catalysed amination reaction



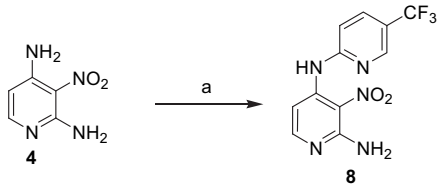
Entry	Metal Source	Ligand	Base	Solvent	2-Coupled/4
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	DMPU	2:1
2	$Pd(OAc)_2$	Xantphos	1 M *t*-BuOLi	DMPU	19:1
3	$Pd(OAc)_2$	*rac*-Binap	1 M *t*-BuOLi	DMPU	1:1
4	$Pd(OAc)_2$	dppb	1 M *t*-BuOLi	DMPU	2:1
5	$Pd(OAc)_2$	PPh_3	1 M *t*-BuOLi	DMPU	1:10
6	$Pd(OAc)_2$	—	1 M *t*-BuOLi	DMPU	1:24
7	$Pd(OAc)_2$	Xantphos	1 M *t*-BuOK	DMPU	17:1
8	$Pd(OAc)_2$	Xantphos	1 M NaHMDS	DMPU	5:1
9	$Pd(dppf)Cl_2$	—	1 M *t*-BuOLi	DMPU	6:1
10	$Pd(OAc)_2$	Xantphos	1 M *t*-BuOLi	1,4-Dioxane	6:1
11	**$Pd(dba)_2$**	**Xantphos**	**1M *t*-BuOK**	**DMPU**	**22:1**
12	$Pd_2(dba)_3$	Xantphos	1 M *t*-BuOK	DMPU	27:1

Table 2
Selective palladium catalysed formation of 2-aryl-4-aminopyridines



Entry	Substrate RX	Yield 2-aryl (%)	Yield 4-aryl (%)	Yield 2,4-bis (%)
1		76	4	10
2		76	2[a]	3[a]
3		71	0	8[a]
4		55	5	10
5		70	8	9
6		46	4[a]	4[a]

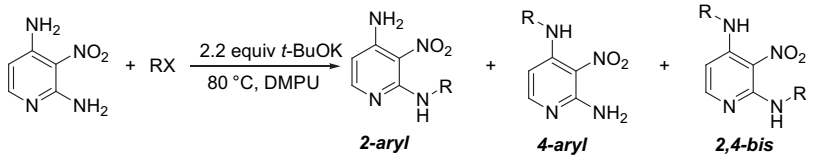
[a] Yield established from crude ^{1}H NMR.

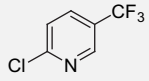
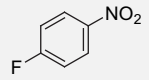
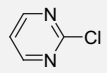
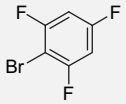
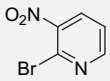


Scheme 4. a) 2-Chloro-5-trifluoromethylpyridine **5**, 2.2 equiv *t*-BuOK, DMPU, 80 °C.

starting material without the need for N-protection. During optimisation we found the regioselective S_NAr reaction proceeded best in polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA). However, a competing N-acylation reaction was observed with these solvents. This unwanted side reaction could be eliminated when we again moved to DMPU as the solvent of choice. The use of 2 equiv of strong base was required to force the reaction to completion since the more acidic product was

Table 3
Selective formation of 4-aryl product



Entry	Substrate RX	Yield 2-aryl (%)	Yield 4-aryl (%)	Yield 2,4-bis (%)
1		1	68	2
2		0	83	0
3		0	64	1[a]
4		0	61	0
5		14[a]	46	0

[a] Yield established from crude ^{1}H NMR.

preferentially deprotonated under the reaction conditions. Again, the formation of 2,4-bisarylated by-products was problematic but could be suppressed by slow addition of the base to the reaction mixture. Using these optimised conditions, a regioisomeric ratio of 65:1 in favour of the 4-aryl isomer was observed. The minor undesired isomer was rejected by crystallisation of the product upon addition of water, providing an isolated yield of 68% of **8**. A range of substrates were subjected to the 4-selective arylation conditions and the reaction was found to be generally applicable. Similar levels of selectivity were observed to that of the optimised lead (Table 3, Entry 1). In the case of the doubly activated 2-bromo-3-nitro pyridine a less selective amination was observed (Table 3, entry 5). This is thought to be due to the differences in the *N*-2 and *N*-4 amine reactivities becoming less important on treatment with more reactive electrophiles.

The structure of the 4-substituted compounds was confirmed by NOE experiments, which showed a correlation between the two aryl rings (Fig. 2). For example, the *p*-nitrophenyl adduct (Table 3, entry 2) showed a 3.9% correlation. No such correlation was observed in the 2-substituted compounds.

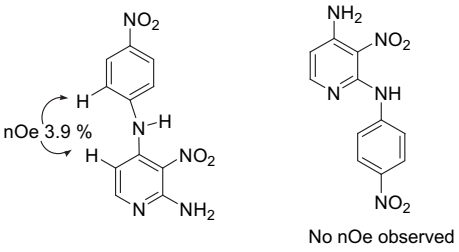
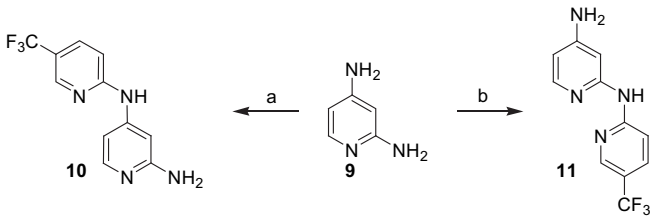


Figure 2.

In order to establish whether the observed regioselectivity of the S_NAr and palladium catalysed cross-coupling reactions was solely a result of the 3-nitro functionality, 2,4-diamino-pyridine **9** was synthesised and subjected to both sets of reaction conditions.[11] The product ratio obtained from the base mediated reaction, although lower in magnitude, was of the same sense as those observed for 2,4-diamino-3-nitropyridine. This lowering in product ratio shows the importance of a suitably positioned electron withdrawing substituent in differentiating between the two amines in the S_NAr reaction, although there is some inherent selectivity for preferential reaction at *N*-4 (Scheme 5). Conversely the pyridine nitrogen directing group for the palladium catalysed *N*-2 substitution is still present in **9**. This allows the reaction to progress with similar product ratios to those seen in the corresponding 3-nitro activated substrate.



Scheme 5. a) 2.2 equiv *t*-BuOK, DMPU 80 °C, 43% (product ratio 3.1:1; **10**/**11**); b) $Pd(dba)_2$·Xantphos, *t*-BuOK, DMPU, 100 °C, 60% (product ratio 1:10; **10**/**11**).

3. Conclusion

In conclusion, we have demonstrated that by judicious choice of reagents, novel and selective arylations of 2,4-diaminopyridines can be effected to afford high yields on mono-arylated products. We envisage that this methodology will be useful for synthetic chemists in both academic and industrial settings, by allowing a rapid entry into complex heterocyclic structures such as those we have described herein, without the need to resort to protecting group strategies.

4. Experimental

4.1. General information

All reactions were carried out under a nitrogen atmosphere, unless otherwise stated. All commercially available reagents and solvents were used as received. Melting points are uncorrected. ^{1}H NMR spectra were recorded using a Bruker DRX 400 MHz spectrometer. Chemical shifts are referenced to residual protons in the deuterated solvent and are quoted in ppm. Coupling constants are quoted in Hz. ^{13}C NMR spectra were recorded on a Bruker 400 MHz (100 MHz) spectrometer with complete proton decoupling. Mass spectrometry was carried out using a Waters LCT—Time of Flight Mass Spectrometer running in positive ion electrospray mode. Flash column chromatography was carried out using 60/silica gel (Davisil® 40–63 micron).

4.2. Typical procedure for Pd cross-coupling: method A

2,4-Diamino-3-nitropyridine (0.25 g, 1.62 mmol), the aromatic halide (1.35 mmol), $Pd(dba)_2$ (0.04 g, 0.07 mmol) and Xantphos (0.04 g, 0.07 mmol) were dissolved/suspended in DMPU (2 mL) under an atmosphere of nitrogen. The flask was evacuated then purged with nitrogen three times. The reaction mixture was heated at 80 °C then treated with a 1.0 M solution of KO^{t}Bu in THF (2.7 mL, 2.7 mmol) over 2 h. The resulting dark red solution was heated at 80 °C until the aromatic halide had been consumed. The reaction was then cooled and diluted with EtOAc followed by water. The phases were separated and the aqueous layer extracted three times with EtOAc. The combined organics were washed with brine three times then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography.

4.3. Typical procedure for S_NAr reactions: method B

2,4-Diamino-3-nitropyridine (0.25 g, 1.62 mmol) and the aromatic halide (1.35 mmol) were dissolved in DMPU (2 mL) under an atmosphere of nitrogen. The flask was evacuated then purged with nitrogen three times. The reaction mixture was heated to 80 °C then treated with a 1.0 M solution of KO^{t}Bu in THF (2.70 mL, 2.70 mmol) over 2 h. The resulting dark red solution was heated at 80 °C until the aromatic halide had been consumed. The reaction was then cooled and diluted with EtOAc followed by water. The phases were separated and the aqueous layer extracted three times with EtOAc. The combined organics were washed with brine three times then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography.

4.3.1. 3-Nitro-N^2-[5-(trifluoromethyl)pyridin-2-yl]pyridine-2,4-diamine: Table 2 entry 1. Prepared by method A, in a 76% isolated yield.

Mp 171–173 °C; ^{1}H NMR (DMSO-d_6) δ_H: 11.09 (1H, s), 8.63 (1H, s), 8.53 (1H, d, J=8.8), 8.22 (2H, s), 8.14 (1H, d, J=8.8), 7.84 (1H, d, J=6.3), 6.54 (1H, d, J=6.3); ^{13}C NMR (DMSO-d_6) δ_C: 149.6, 147.3, 144.4, 143.9, 140.8, 132.2, 123.4, 118.7 (q, J_{CF}=272.0), 116.9, 112.7, 106.9; HRMS (ESI$^+$) calcd for $C_{11}H_8F_3N_5O_2$ 300.0708, found 300.0703.

4.3.2. 3-Nitro-N,N′-bis[5-(trifluoromethyl)pyridin-2-yl]pyridine-2,4-diamine: Table 2 entry 1. Prepared by method A, in a 10% isolated yield.

Mp 194–195 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.21 (1H, s), 10.20 (1H, s), 8.60 (1H, s), 8.56 (1H, s), 8.35 (1H, d, J=5.7), 8.11 (1H, d, J=9.0),

8.10 (1H, d, J=9.0), 7.95 (1H, d, J=9.0), 7.75 (1H, d, J=5.7), 7.33 (1H, d, J=9.0); ^{13}C NMR (DMSO-d_6) δ_C: 156.4, 156.3, 151.1, 147.6, 145.5, 145.3, 143.3, 136.1, 135.9, 126.5, 126.0, 123.4 (q, J_{CF}=272.0), 123.3 (q, J_{CF}=272.0), 119.2, 114.0, 112.7, 111.0; HRMS (ESI$^+$) calcd for $C_{17}H_{10}F_6N_6O_2$ 445.0848, found 445.0847.

4.3.3. 3-Nitro-N^2-[4-(trifluoromethyl)phenyl]pyridine-2,4-diamine: Table 2 entry 2. Prepared by method A, in a 76% isolated yield.

Mp 174–176 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.57 (1H, s), 8.18 (2H, s), 7.93 (2H, d, J=8.6), 7.76 (1H, d, J=5.9), 7.65 (2H, d, J=8.6), 6.41 (1H, d, J=5.9); ^{13}C NMR (DMSO-d_6) δ_C: 153.3, 151.3, 149.9, 143.4, 126.3, 126.1, 123.5 (q, J_{CF}=272.0), 121.9, 117.7, 105.6; HRMS (ESI$^+$) calcd for $C_{12}H_9F_3N_4O_2$ 299.0756, found 299.0745.

4.3.4. 3-Nitro-N^2-(4-nitrophenyl)pyridine-2,4-diamine: Table 2 entry 3. Prepared by method A, in a 71% isolated yield.

Mp 244–246 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.65 (1H, s), 8.19 (2H, d, J=9.2), 8.15 (2H, s), 7.98 (2H, d, J=9.2), 7.81 (1H, d, J=5.8), 6.49 (1H, d, J=5.8); ^{13}C NMR (DMSO-d_6) δ_C: 153.0, 150.5, 149.4, 146.4, 141,8, 125.1, 120.7, 118.4, 106.6; HRMS (ESI$^+$) calcd for $C_{11}H_9N_5O_4$ 276.0733, found 276.0734.

4.3.5. 3-Nitro-N^2-pyridin-2-ylpyridine-2,4-diamine: Table 2 entry 4 and 5. Prepared by method A, in a 55 & 70% isolated yield, respectively.

Mp 179–181 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.97 (1H, s), 8.43 (1H, d, J=8.4), 8.30 (1H, m), 8.26 (2H, s), 7.80 (2H, m), 7.09–7.05 (1H, m), 6.45 (1H, d, J=6.0); ^{13}C NMR (DMSO-d_6) δ_C: 153.4, 152.7, 150.5, 149.8, 148.5, 138.5, 119.2, 117.6, 114.9, 105.8; HRMS (ESI$^+$) calcd for $C_{10}H_9N_5O_2$ 232.0834, found 232.0826.

4.3.6. 3-Nitro-N^4-(pyridin-2-yl)pyridine-2,4-diamine: Table 2 entry 4 and 5. Prepared by method A, in a 5 & 8% isolated yield, respectively.

Mp 181–183 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.49 (1H, s), 8.34 (1H, m), 7.94 (1H, d, J=5.9), 7.79 (1H, m), 7.71 (2H, s), 7.51 (1H, d, J=5.9), 7.23 (1H, d, J=8.2), 7.10 (1H, m); ^{13}C NMR (DMSO-d_6) δ_C: 156.0, 153.9, 153.2, 148.1, 146.2, 139.0, 119.3, 118.5, 115.7, 101.8; HRMS (ESI$^+$) calcd for $C_{10}H_9N_5O_2$ 232.0834, found 232.0836.

4.3.7. 3-Nitro-N,N′-di(pyridin-2-yl)pyridine-2,4-diamine: Table 2 entry 4 and 5. Prepared by method A, in a 10 & 9% isolated yield, respectively.

Mp 113–115 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.20 (2H, s), 8.30 (2H, m), 8.19 (1H, d, J=5.9), 8.11 (1H, d, J=8.4), 7.81 (2H, m), 7.70 (1H, d, J=5.9), 7.25 (1H, d, J=8.4), 7.14–7.05 (2H, m); ^{13}C NMR (DMSO-d_6) δ_C: 152.9, 152.7, 151.1, 149.1, 148.0, 145.6, 139.1, 138.8, 122.3, 119.5, 119.0, 117.5, 115.6, 114.5, 107.1; HRMS (ESI$^+$) calcd for $C_{15}H_{12}N_6O_2$ 309.1100, found 309.1104.

4.3.8. 3-Nitro-N^2-(5-nitropyridin-2-yl)pyridine-2,4-diamine: Table 2 entry 6. Prepared by method A, in a 46% isolated yield.

Mp 250–252 °C; ^{1}H NMR (DMSO-d_6) δ_H: 11.21 (1H, s), 9.09 (1H, s), 8.59 (1H, d, J=2.7), 8.45 (1H, J=2.7), 8.17 (2H, s), 7.88 (1H, d, J=5.9), 6.60 (1H, d, J=5.9); ^{13}C NMR (DMSO-d_6) δ_C: 156.9, 152.8, 149.1, 149.0, 145.4, 139.3, 134.4, 119.5, 112.8, 108.1; HRMS (ESI$^+$) calcd for $C_{10}H_8N_6O_4$ 277.0685, found 277.0684.

4.3.9. 3-Nitro-N^4-[5-(trifluoromethyl)pyridin-2-yl]pyridine-2,4-diamine: Table 3 entry 1. Prepared by method B, in a 68% isolated yield.

Mp 250–252 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.48 (1H, s), 8.80 (1H, s), 8.07 (1H, dd, J=8.8 & 2.4), 8.04 (1H, d, J=5.9), 7.53 (2H, s), 7.39 (1H, d, J=5.9), 7.30 (1H, d, J=8.8). ^{13}C NMR (DMSO-d_6) δ_C: 156.5, 155.3, 153.6, 145.4, 144.3, 135.9, 120.3, 119.3, 113.0, 114.3, 114.1; HRMS (ESI$^+$) calcd for $C_{11}H_8F_3N_5O_2$ 300.0708, found 300.0709.

4.3.10. 3-Nitro-N^4-(4-nitrophenyl)pyridine-2,4-diamine: Table 3 entry 2. Prepared by method B, in a 83% isolated yield.

Mp 251–253 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.11 (1H, s), 8.25 (2H, d, J=9.0), 7.91 (1H, d, J=5.8), 7.75 (2H, s), 7.53 (2H, d, J=9.0), 6.48 (1H, d, J=5.8); ^{13}C NMR (DMSO-d_6) δ_C: 156.1, 153.9, 147.3, 146.3, 143.3, 125.7, 122.7, 119.1, 100.9; HRMS (ESI$^+$) calcd for $C_{11}H_9N_5O_4$ 276.0733, found 276.0734.

4.3.11. 3-Nitro-N^4-pyrimidin-2-ylpyridine-2,4-diamine: Table 3 entry 3. Prepared by method B, in a 64% isolated yield.

Mp 190–192 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.99 (1H, s), 8.66 (2H, d, J=4.7), 8.08 (1H, d, J=5.5), 7.86 (1H, d, J=5.5), 7.83 (2H, s), 7.15 (1H, t, J=4.7); ^{13}C NMR (DMSO-d_6) δ_C: 159.0, 158.8, 156.0, 154.6, 144.9, 118.9, 116.2, 102.9; HRMS (ESI$^+$) calcd for $C_9H_8N_6O_2$ 233.0787, found 233.0792.

4.3.12. N^4-(2-Bromo-3,5-difluorophenyl)-3-nitropyridine-2,4-diamine: Table 3 entry 4. Prepared by method B, in a 61% isolated yield.

Mp 246–248 °C; ^{1}H NMR (DMSO-d_6) δ_H: 10.19 (1H, s), 7.97 (2H, s), 7.80 (1H, d, J=6.0), 7.49 (1H, m), 7.38 (1H, m), 5.94 (1H, d, J=6.0); ^{13}C NMR (DMSO-d_6) δ_C: 156.5, 154.2, 149.1, 140.3 (dd, J_{CF}=259.1, 12.0), 117.2, 111.7 (dd, J_{CF}=255.1, 12.0), 110.0, 109.6, 104.2, 103.8, 99.0; HRMS (ESI$^+$) calcd for $C_{11}H_7BrF_2N_4O_2$ 344.9799, found 344.9789.

4.3.13. 3-Nitro-N^4-(3-nitropyridin-2-yl)pyridine-2,4-diamine: Table 3 entry 5. Prepared by method B, in a 46% isolated yield.

Mp 240–242 °C; ^{1}H NMR (DMSO-d_6) δ_H: 12.26 (1H, s), 8.68 (2H, m), 8.12 (1H, d, J=5.8), 7.86 (1H, d, J=5.8), 7.81 (2H, s), 7.32 (1H, dd, J=8.4, 4.5); ^{13}C NMR (DMSO-d_6) δ_C: 155.9, 154.5, 154.1, 147.5, 144.0, 136.4, 133.1, 119.6, 118.7, 104.5; HRMS (ESI$^+$) calcd for $C_{10}H_8N_6O_4$ 277.0685, found 277.0687.

*4.3.14. N^4-[5-(Trifluoromethyl)pyridin-2-yl]pyridine-2,4-diamine: **10**.* Prepared by method B, in a 43% isolated yield as a mixture of isomers. An analytically pure sample was provided by preparative HPLC.

^{1}H NMR (CD_3OD) δ_H: 8.65 (1H, s), 8.09 (1H, dd, J=9.6, 4.4), 7.81 (1H, d, J=7.2), 7.16 (1H, d, J=8.8), 6.55 (1H, dd, J=6.8, 1.6), 6.32 (1H, d, J=1.8); ^{13}C NMR (CD_3OD) δ_C: 160.2, 149.1, 143.9, 143.8, 136.0, 135.9, 135.6, 120.5, 112.2, 105.5, 92.0; HRMS (ESI$^+$) calcd for $C_{11}H_9F_3N_4$ 255.0858, found 255.0851.

*4.3.15. N^2-[5-(Trifluoromethyl)pyridin-2-yl]pyridine-2,4-diamine: **11**.* Prepared by method A, in a 61% isolated yield as a mixture of isomers. An analytically pure sample was provided by preparative HPLC.

^{1}H NMR (CD_3OD) δ_H: 8.61 (1H, s), 8.01 (1H, s,), 7.96 (1H, dd, J=9.0, 1.9), 7.66 (1H, d, J=8.0), 7.10 (1H, d, J=8.4), 6.86 (1H, dd, J=7.2, 2.0); δ_C: 157.0, 145.08, 144.7, 143.91, 136.0, 134.7, 131.0, 125.44, 116.7, 112.3, 95.2; HRMS (ESI$^+$) calcd for $C_{11}H_9F_3N_4$ 255.0858, found 255.0850.

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