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Abstract

We report a two step one-pot method for the synthesis of 2-bromo-6-aryl[5*H*]pyrrolo[2,3-*b*]pyrazines. The process makes use of a cleaner copper-free Sonogashira coupling and an improved base-mediated 5-*exo*-dig cyclisation to afford the products in good yields. This method expands the scope to structures that are poorly represented in literature and incorporates a halide for further synthetic elaboration.

Key Words

Sonogashira
Cyclisation
Kinase

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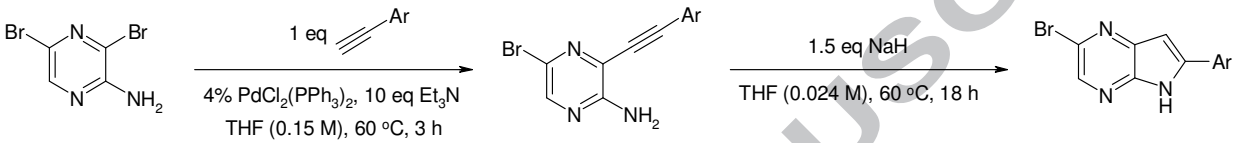

Abstract

We report a two step, one-pot method for the synthesis of 2-bromo-6-aryl[5*H*]pyrrolo[2,3-*b*]pyrazines. The process makes use of a copper-free Sonogashira coupling and an improved base-mediated 5-*exo*-dig cyclisation to afford the products in good yields. This method expands the scope to structures that are of importance in both synthetic and medicinal chemistry and incorporates a halide for further synthetic elaboration.

Key Words

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Pyrrolo[2,3-*b*]pyrazines are important molecular structures for drug discovery. This is particularly relevant in the area of kinase inhibition, where they have been shown to compete with ATP for binding to the kinase active site.[1-5]

During a recent medicinal chemistry program we became interested in the synthesis of 2-bromo-6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazine (**1)** (Figure 1) as a key building block for further elaboration. Whilst the synthesis of 6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazines has been reported, this approach did not allow inclusion of the bromine atom that was required for the convergent synthesis of our target molecules.

Previous in-house syntheses of pyrrolo[2,3-*b*]pyrazines have employed 5-bromo-3-ethynylpyrazin-2-amines and their subsequent treatment with base to affect cyclisation to form the desired bicycle (Scheme 1). This approach is well documented in the literature for both pyrrolo[2,3-*b*]pyrazines and other related bicyclic structures,[6-8] but does not include any examples where the product pyrrolo[2,3-*b*]pyrazine has a phenyl ring at the 6-position. The synthesis of 6-(3-indolynyl)[5*H*]pyrrolo[2,3-*b*]pyrazines has been reported,[9] however, not only did we think that further work was warranted - as bourne out by our initial results - on 6-phenyl systems, but it was thought that the 5-bromo substituent in our model system would affect the cyclisation and require its own optimum conditions. Herein, we report our attempts to develop a general method for the synthesis of 6-phenyl systems.

The initial strategy involved the synthesis of the required cyclisation precursor, 5-bromo-3-(phenylethynyl)pyrazin-2-amine **2**, which was achieved through regioselective Sonogashira coupling of readily available 2-amino-3,5-dibromopyrazine and ethynylbenzene (Scheme 2). Later attempts at this reaction on both the parent compound and substituted analogues were found to be successful in the absence of any copper catalyst (Table 1), and this modification achieved higher isolated yields in most cases, through easier reaction work-up and purification. Attempts were also made at reducing the equivalents of triethylamine, but the inconsistent yields produced with fewer equivalents, along with the low cost and ease

of removal of the excess reagent, meant that 10 equivalents could be employed. The reaction was also found to be tolerant of a range of solvents and temperatures, with the ideal combination of THF and 60 °C allowing ease of work-up and an efficient reaction time respectively, whilst minimising by-product formation.

Calculations show that the LUMO of 2-amino-3,5-dibromopyrazine is not evenly distributed around the pyrazine ring and has a greater presence around the 3-position (Figure 2). We postulate that this, along with potential pre-coordination of the palladium catalyst to the amino group, gave rise to the high degree of selectivity observed for the Sonogashira coupling. Reaction at C-5 of 2-amino-3,5-dibromopyrazine was only observed with excess alkyne once the desired substitution at C-3 had taken place. This 3,5-bis(phenylethynyl)pyrazin-2-amine impurity **3** could be effectively eliminated through careful addition of the alkyne reagent, and any by-products that were formed could be easily removed by standard chromatography techniques.

The initial attempt at cyclising **2** (entry 1, Table 2) employed standard conditions for the reaction of 5-bromo-3-ethynylpyrazin-2-amines bearing a simple alkyl group.[9] Monitoring the reaction proved difficult due to the co-elution of the starting material and the product in LCMS and TLC analyses, and the isolated sample contained an inseparable mixture of these two components in low yield. Increasing the reaction time (entry 2, Table 2) gave complete conversion and also improved the yield modestly. Changing the solvent from NMP to THF necessitated a slight lowering of the reaction temperature and was intended to allow easier work-up of the reaction mixtures. This modification also resulted in a higher yield (entry 3, Table 2). Employing the stronger base sodium hydride (entry 4, Table 2) also improved the reaction, presumably by achieving more complete and effective deprotonation of the starting material, and also by ultimately giving a cleaner crude reaction mixture.

Whilst these early improvements in yield were seen as encouraging, attempts to obtain a product of higher yield and purity using a lower reaction temperature, the addition

of more base and the use of different purification techniques (entries 5-9, Table 2) gave varying degrees of success with respect to the isolated yield. However, reducing the reaction concentration (entry 10, Table 2) gave a significant and readily reproducible improvement.

Scheme 3 and Table 3 summarise the application of our optimised conditions for both the Sonogashira and cyclisation reactions on a number of substituted phenyl and heteroaryl analogues. Synthetically useful yields were obtained in most cases showing that this method is of general use. The largest single contributing factor to the lowering of the isolated yield was the solubility of the final compound and its behaviour during chromatography. Certain analogues produced better results when purified by trituration methods, but in order to obtain high purity samples for analysis and to provide a consistent representative yield for comparison purposes, all yields quoted are for samples obtained after silica gel column chromatography.

Notable results are those for the *ortho*-nitrophenyl and *para*-methyl benzoate (entries 5 and 16, respectively), which gave poor results in both Sonogashira and cyclisation reactions. Whilst the result for *ortho*-nitrophenyl is a puzzling discrepancy, particularly in comparison to the other nitrated analogues (entries 10 and 15), the loss of desired product from the methyl ester was found to be caused by hydrolysis to the corresponding carboxylic acid.

The fact that both the Sonogashira and cyclisation reactions are performed in the same solvent presented a potential useful opportunity for telescoping them together into a convenient one-pot procedure. The only practical considerations to be addressed were the differing concentrations of the two reactions and the need for anhydrous conditions for the cyclisation. For development of this process we went back to the model system of reacting 2-amino-3,5-dibromopyrazine with ethynylbenzene, and subsequent cyclisation to form **1**.

Our initial conditions involved performing the Sonogashira reaction at the lower concentration required for optimum cyclisation, with the practical benefit that the reaction

mixture would only require cooling to ambient temperature and the addition of sodium hydride as the manipulations between reactions. This resulted in an appreciably slower Sonogashira reaction (~90% complete after 7 hours by LC-MS) and gave a slightly lower yield of product **1** of 62%, partly due to the more difficult purification.

In an attempt to achieve the rapid and complete conversion seen in earlier Sonogashira reactions, our second attempt involved carrying out this step at its original concentration and then transfering the crude reaction mixture into a larger flask and evaporating to dryness. This could then be redissolved in a larger volume of THF to give the optimum concentration for the cyclisation step. This approach not only involved more practical manipulation between stages, but also resulted in a significantly lower yield of **1** of 44%. This was most likely due to a failure to create optimum cyclisation conditions from the mixture transfer.

Our third attempt also involved carrying out the Sonogashira reaction at its original concentration, followed by simply adding more solvent to the same reaction vessel to achieve the concentration required for the optimum cyclisation. This process gave an improved yield of **1** of 64%. Whilst this one-pot procedure did not produce quite as high a yield of cyclised product as the original two-step process (71% over two steps), there are clear advantages to the synthetic chemist in terms of time saved and purification steps avoided, which makes the one-pot procedure a preferable option.

The final column in Table 3 shows the yields for the one-pot procedure on all the original analogues. Again, all the yields are quoted for material isolated after silica gel column chromatography and are generally equal to, or higher than, the overall yield obtained by performing the two steps separately. As poor reactants for this process, entries 5 and 16 still present discrepancies from the other analogues, the methyl ester proving to be completely unstable to the reaction conditions for telescoping.

In conclusion, this methodology provides a facile and versatile one-pot approach to 2-bromo-6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazines, for further elaboration into useful

drug-like molecules. The remaining bromine atom in the product provides a useful functional group for subsequent synthetic manipulations and our method has been developed with this in mind. Access to the corresponding des-bromo analogues would be desirable in certain cases, but is not achieved readily from the logical 2-amino-3-bromopyrazine starting material. This reagent is significantly more expensive and less readily available than the dibromide used here. However, in order to demonstrate access to these moieties, we have successfully carried out debromination[10] of parent **1** (Scheme 4) in good yield.

Supplementary data

Supplementary data (general and optimised synthetic procedures, ^{1}H and ^{13}C NMR, IR and mass spectrometry data) associated with this article can be found, in the online version, at

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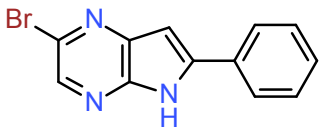

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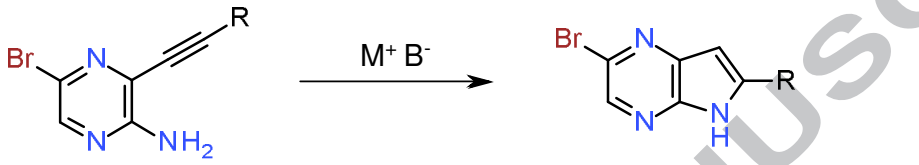
Figure 1. 2-Bromo-6-phenyl[5*H*]pyrrolo[2,3-*b*]pyrazine (**1**)



Scheme 1. Base-mediated cyclisation of 5-bromo-3-ethynylpyrazin-2-amine

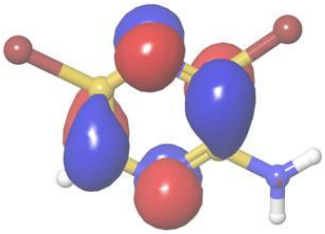
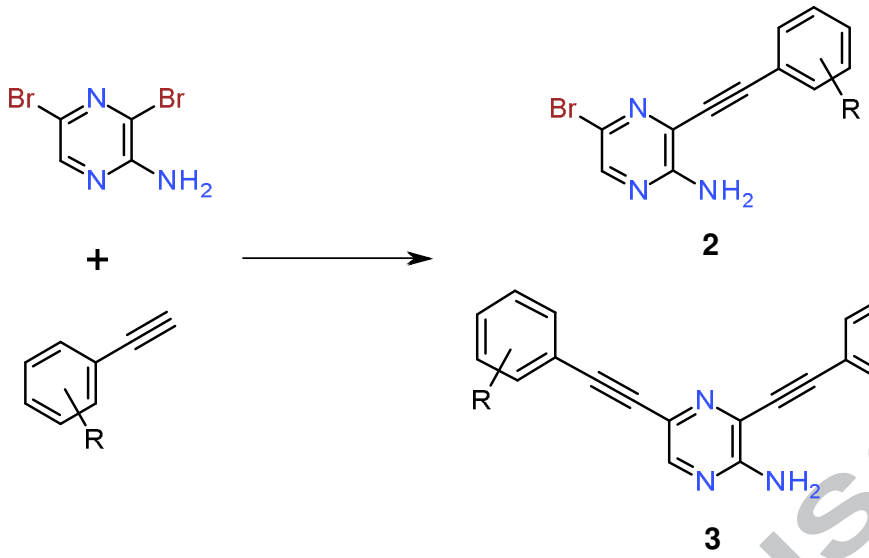
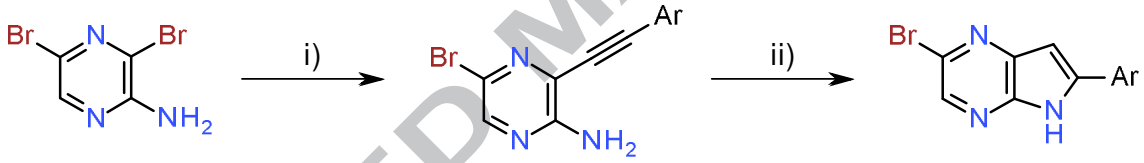


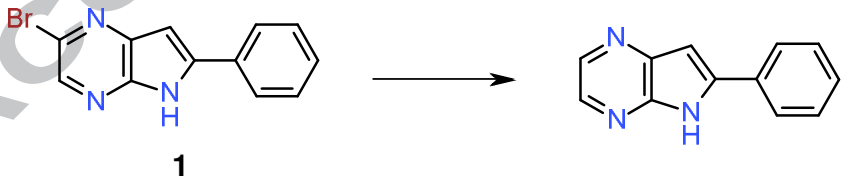
Figure 2. The LUMO density map of 2-amino-3,5-dibromopyrazine



Scheme 2. Synthesis of 5-bromo-3-(arylethynyl)pyrazin-2-amines *via* Sonogashira coupling. Reagents and conditions: $PdCl_2(PPh_3)_2$ (0.04 equiv), Et_3N (10 equiv).



Scheme 3. Optimisied conditions for the Sonogashira coupling and cyclisation. Reagents and conditions: (i) alkyne (1 equiv), $PdCl_2(PPh_3)_2$ (0.04 equiv), Et_3N (10 equiv), THF (0.15 M), 60 °C, 3 h; (ii) NaH (1.5 equiv), THF (0.024 M), 60 °C, 18 h.



Scheme 4. Silane-mediated hydrodehalogenation of **1**. Reagents and conditions: $Pd_2(dba)_3$ (0.05 equiv), S-Phos (0.05 equiv), Et_3SiH (5 equiv), Et_3N (2 equiv), 1,4-dioxane, 89% yield.

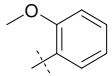
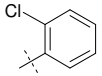
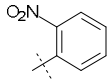
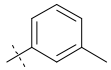
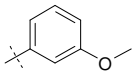
Table 1. Optimising the Sonogashira reaction between 2-amino-3,5-dibromopyrazine and ethynylbenzene.

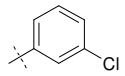
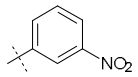
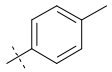
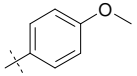
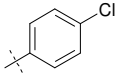
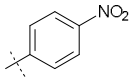
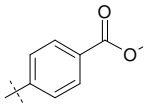
Entry	Alkyne (equiv)	CuI (equiv)	Conc (M)	Solvent	Temp (°C)	Time (h)	Yield of **2** (%)	Yield of **3** (%)
1	1.2	0.12	0.22	DMF	120	0.17	52	-
2	1.2	0.12	0.22	DMF	100	0.17	67	29
3	1.0	0.10	0.15	THF	60	2.00	69	0
4	1.0	0.00	0.15	THF	60	2.00	82	0

Table 2. Optimising the cyclisation of 5-bromo-3-(phenylethynyl)pyrazin-2-amine **2**.

Entry	Base (equiv)	Solvent	Conc (M)	Temp (°C)	Time (h)	Quench reagent	Purification method	Yield (%)
1	KO^tBu (1.0)	NMP	0.2	80	1.5	sat. NH_4Cl	aq work-up and silica column	6 (1.8:1 mix of **2** and **1**)
2	KO^tBu (1.0)	NMP	0.2	80	18	sat. NH_4Cl	aq work-up	26
3	KO^tBu (1.0)	THF	0.2	70	18	sat. NH_4Cl	aq work-up	40
4	NaH (1.0)	THF	0.2	70	18	sat. NH_4Cl	aq work-up	55
5	NaH (1.0)	THF	0.2	70	18	sat. NH_4Cl	aq work-up and trituration in MeCN	37
6	NaH (1.0)	THF	0.2	60	18	sat. NH_4Cl	aq work-up and trituration in CH_2Cl_2	45
7	NaH (1.0)	THF	0.2	60	18	AcOH	aq work-up and trituration in CH_2Cl_2	63
8	NaH (1.25)	THF	0.2	60	18	HCl	aq work-up and silica column	17
9	NaH (1.25)	THF	0.2	60	18	-	aq work-up and trituration in CH_2Cl_2	80
10	NaH (1.5)	THF	0.024	60	18	H_2O	silica column	86

Table 3. Main Results.

Entry	Ar[a]	Yield of Sonogashira reaction (%)	Yield of cyclisation reaction (%)	Combined yield of the two-step reaction (%)	Yield of the one-pot procedure (%)
1		82	86	71	64
2		80	77	62	67
3		40	63	25	42
4		42	68	29	55
5		14	0	0	0
6		48	33	16	55
7		89	74	66	54
8		80	61	49	56

9		89	81	72	46
10		75	49	37	30
11		62	32	20	59
12		81	82	66	74
13		75	68	51	48
14		73	54	39	61
15		47	48	23	33
16		53	34	18	0
17		44	40	18	22

18		54	83	45	79
19		92	98	90	80

[a] See Scheme 3.