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Preparation of differentially substituted 3,6-diaminopyridazines under mild conditions

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ABSTRACT

Although desirable from a medicinal chemistry perspective, the differentially substituted 3,6-diaminopyridazine moiety is a highly challenging target using current literature approaches. Recent methods of Ullmann-type couplings are evaluated and a mild route to prepare these structures from iodide precursors is presented.

Pyridazine-based structures have long been attractive targets for many medicinal chemistry projects as they are associated with a number of advantageous properties for drug-like molecules. Isosteric replacement of various aromatic substituents such as phenyl and pyridyl with a pyridazine ring leads to a desirable lowering of lipophilicity, which also tends to improve aqueous solubility.[1] Furthermore, the H-bond acceptor properties of these diazine analogues can result in the creation of new interactions and binding opportunities with drug receptors.[2] In particular, 3-aminopyridazines have been targeted due to their ability to act as surrogates for ester,[3] carboxamide[4] and amine[5] functionalities. In addition, this molecular fragment is known to be a privileged structure in neuropharmacology[6] having been beneficial to research in the areas of GABA antagonists,[7] AChE inhibitors,[8] M1 agonists[9] and DAPK inhibitors.[10]

It is unsurprising therefore that the 3,6-diaminopyridazine moiety has also proven to be a component of multiple drug discovery programs, appearing as the central focus of several projects[2,11] and in the marketed antihypertensive agent, cadralizine (Fig. 1). 3,6-Diaminopyridazines have also been included as part of the scope of many patents and have been used as key intermediates leading to a variety of other pharmaceutically important compounds.[12]

However, despite the potential of these molecules, the synthetic accessibility of the 3,6-diaminopyridazine scaffold is still problematic using existing methodology. In particular, the analogues derived from primary and secondary amines remain extremely challenging targets in the absence of mild, high yielding synthetic methods. Of specific interest to us were *N*-alkyl-substituted analogues of diaminopyridazine **2** (R^1 = alkyl, R^2 = H), where potential routes were typified by the high temperature nucleophilic displacement of a halogen atom (X) from an aminohalopyridazine **1** (Scheme 1). The poor reactivity of 'X' in these

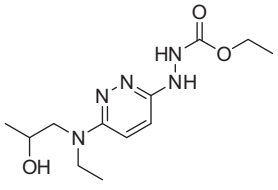
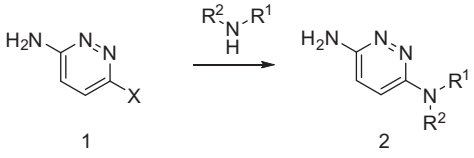


Figure 1. Cadralizine.



Scheme 1. S_NAr displacement route to diaminopyridazines.

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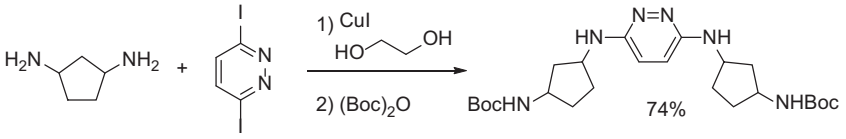


Scheme 2. Krische and Gong's synthesis.

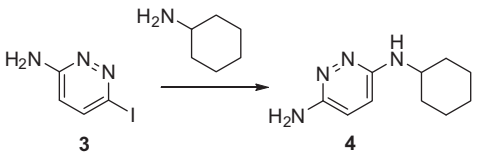
structures effectively limits the scope of this method to cyclic secondary amines (where excess or neat amine is often required and temperatures range typically from 100 to 200 °C).[13] For cyclic amines, these extreme conditions mean that many functional groups are not well tolerated. Similarly, the few reported literature examples of displacements involving primary amines have necessitated the use of forcing conditions and reported yields are low.[14]

Alternative approaches have included several examples from the patent literature where metal-catalysed C—N bond formation reactions using palladium have resulted in low to moderate yields of the desired diaminopyridazine targets. These have mostly focused on the introduction of anilines with alkyl amines being poorly precedented.[15] Although copper catalysis has on a limited number of occasions been used to promote the reaction of amino-halopyridazines with 'NH' heterocycles,[16] a search of the literature revealed only a single example where the methodology had been extended to include an amine as a reactant. In 2005, Krische and Gong reported the synthesis of a symmetrically substituted diaminopyridazine in good yield using CuI in conjunction with ethylene glycol as the ligand (Scheme 2).[17] The step in question using diiodopyridazine as the starting material employed a sixfold excess of the displacing amine (this product was also isolated as the di-Boc protected compound).

To the best of our knowledge, other combinations of ligands and copper salts have not been investigated. Given the recent developments in copper-catalysed C—N bond formation, and our interest in compounds containing differentially substituted 3,6-diaminopyridazines, we decided to explore the potential of this approach to address the synthetic issues mentioned above.

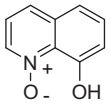
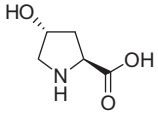
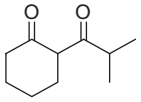
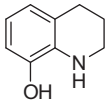
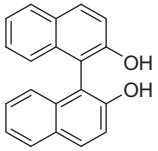
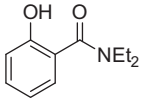
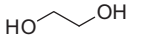
We chose to employ iodoaminopyridazine **3** as the substrate for this work, which would be readily accessible[18] and also well-suited to the copper-catalysed method. Using the coupling of **3** and aminocyclohexane as a trial reaction (Scheme 3), we first assessed a range of potential copper-catalysed approaches chosen from recent literature examples of Ullmann-type C—N bond formation.[19] These were taken from general methods involving the reactions between amines and aryl bromides or iodides. Unlike the majority of these studies we felt it desirable to employ an excess of the aryl halide and have the amine as the limiting reagent; the coupling conditions were therefore adjusted accordingly.

Results (with isolated yields) are summarised in Table 1 and show that although the desired target was formed on each occasion the corresponding recoveries were low, ranging from 8% to 31%. The methods giving the highest yields of **4** were the example based on the studies of Ma[19e] using CuI together with L-hydroxyproline as a ligand (entry 2), and similarly the CuI combination with a cyclic β-diketone (entry 3). Using these conditions, we were able to isolate 31% and 28% yields, respectively, of target **4**. It is also worth noting that the method derived from Krische and Gong's successful transformation (discussed in the introduction above) led to a very low recovery of **4** (8%, see entry 7).



Scheme 3. Trial reaction for Ullmann-type coupling.

Table 1
Assessment of Ullmann-type methods[a]

Entry	Ligand	Cu(I)	Base	Temp (°C)	Yield (%)
1		CuBr	Cs_2CO_3	20	21
2		CuI	K_2CO_3	50	31
3		CuI	Cs_2CO_3	20	28
4		CuBr	Cs_2CO_3	90	18
5		CuBr	K_3PO_4	20	22
6		CuI	K_3PO_4	90	10
7		CuI	K_3PO_4	95	8

[a] Reactions performed with 1.2 equiv of **3**.

Table 2
Optimisation of the reaction conditions

Entry	Base	Cu(I)	Solvent	Ligand	Yield (%)
1	K_2CO_3	CuI	DMSO	L-Hydroxyproline	31
2	Cs_2CO_3	CuI	DMSO	L-Hydroxyproline	12
3	K_3PO_4	CuI	DMSO	L-Hydroxyproline	72[a] 78[b] 81[c]
4	K_3PO_4	CuI	DMSO	L-proline	68
5	K_3PO_4	CuI	DMSO	*N*,*N*-Dimethylglycine	60
6	K_3PO_4	CuBr	DMSO	L-Hydroxyproline	70
7	K_3PO_4	CuCN	DMSO	L-Hydroxyproline	64
8	K_3PO_4	CuI	DMF	L-Hydroxyproline	42
9	K_3PO_4	CuI	DMSO	—	29

Conditions:
[a] 1.2 equiv of **3**.
[b] 1.3 equiv of **3**.
[c] 1.5 equiv of **3**.