Facile synthesis of 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines

Joanna Wlochal, Andrew Bailey

PII: S0040-4039(15)30272-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.10.075
Reference: TETL 46904

To appear in: *Tetrahedron Letters*

Received Date: 18 September 2015
Revised Date: 10 October 2015
Accepted Date: 23 October 2015

Please cite this article as: Wlochal, J., Bailey, A., Facile synthesis of 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.10.075

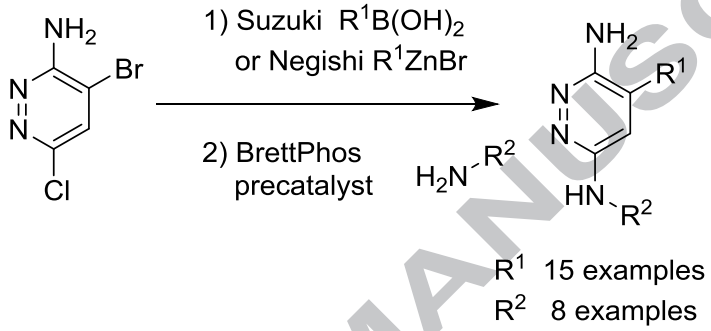
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Facile synthesis of 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines

Leave this area blank for abstract info.

Joanna Wlochal, Andrew Bailey.



Tetrahedron Letters
journal homepage: www.elsevier.com

Facile synthesis of 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines.

Joanna Wlochal, Andrew Bailey*

AstraZeneca Pharmaceuticals, Oncology iMed, Alderley Park, Macclesfield, Cheshire, SK10 4TG.

** a.bailey@redxpharma.com*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

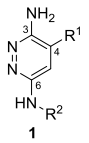
Keywords:
Substituted pyridazine-3,6-diamines
3,6-diaminopyridazines
Brettphos precatalyst
Buchwald protocol

ABSTRACT

Substituted pyridazine-3,6-diamines are attractive but poorly precedented scaffolds in medicinal chemistry and are challenging targets in terms of synthetic tractability. In the following communication we report the use of a Buchwald protocol for the facile synthesis of 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines. This approach utilises the unreactive nature of the pyridazine 3-amino group, negating the need for an additional protecting group in the transformation. The relevant precursors were prepared by selective Suzuki or Negishi transformations using commercially available 4-bromo-6-chloro-3-pyridazinamine.

The pyridazine-3,6-diamine scaffold has been explored in multiple drug discovery programs, appearing as a key focus of several projects[1] and resulting in, for example, the marketed antihypertensive agent, cadralazine.[2] Pyridazine-3,6-diamines have also served as a broad synthetic platform in many patents and have been used as key intermediates leading to a variety of other pharmaceutically important compounds.[3]

As part of an AstraZeneca ongoing interest in the medicinal chemistry of pyridazine-3,6-diamines, we wished to investigate the effect of either aryl or alkyl substituents (R^1) directly introduced onto the heterocyclic core. Particularly desirable targets for our studies were the 4-substituted, N^6-alkylated, analogues of pyridazine-3,6-diamines such as **1**



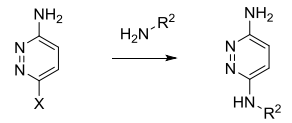
1

Figure 1. Substituted pyridazine-3,6-diamine targets

However, synthetic entry to targets containing the pyridazine-3,6-diamine motif is limited. Described methods rely on high temperature nucleophilic displacement of a halogen atom (X) from an aminohalopyridazine (Figure 2).[4] The poor reactivity of X in these structures effectively limits the scope of this method to cyclic secondary amines (where excess or neat amine is often required and temperatures typically range from 100 to 200 °C). Similarly, the few reported literature examples of displacements involving primary amines have necessitated the use of forcing conditions and resulted in poor yields.[5]

A search of the literature also revealed that, despite the large number of publications focussed on pyridazine-3,6-diamines (where R^1 = H), structures such as **1**, carrying additional alkyl or aryl substituents (R^1) were very poorly represented. Furthermore, to the best of our knowledge no route to make these substituted analogues had been reported.

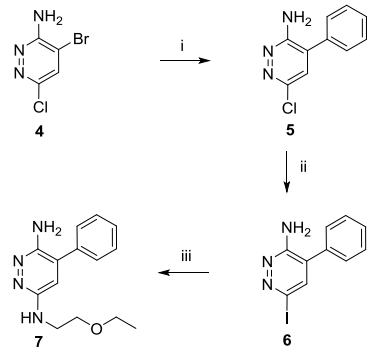
In our previous publication,[6] we had already demonstrated that transformation of the corresponding unsubstituted analogues could be accomplished under mild conditions, by utilising a copper catalysed, Ullmann-type methodology and the appropriate iodo precursor **2a** (Figure 2). Building on this report, we initially hoped to extend the scope of our work by including suitable R^1 substituted substrates to allow access to the corresponding analogues exemplified by **1**.



2a, X = I **3**

Figure 2. Displacement routes to pyridazine-3,6-diamines

With this in mind, our initial strategy relied on the application of commercially available 4-bromo-6-chloro-3-pyridazinamine **4** as a suitable starting material. In order to assess its reactivity profile in a standard Suzuki coupling reaction, we performed a tentative experiment with **4**, phenylboronic acid, $Pd(dppf)Cl_2$ catalyst and sodium carbonate as a base in refluxing 1,4-dioxane to access **5** in good yield (71%). To test and further advance this approach we then subjected the resulting substrate **5** to our previously developed amination protocol. Using this strategy we were able to synthesise pyridazine-3,6-diamine **7** in 65% yield by sequential preparation of the corresponding iodo intermediate **6** followed by copper catalysed Ullmann-type coupling (Scheme 1).



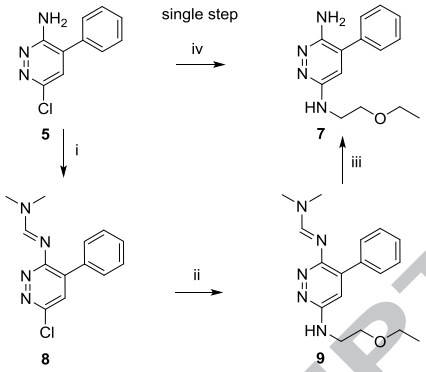
Scheme 1. Reaction conditions: (i) 1.03 equiv. $PhB(OH)_2$, $Pd(dppf)Cl_2.CH_2Cl_2$ (10 mol%), Na_2CO_3, aq. dioxane, reflux, 71% (ii) HI (aq., 57 wt%), 127 °C, 94% (iii) 1.3 equiv. 2-ethoxyethanamine, CuI (10 mol%), L-hydroxyproline (20 mol%), 3 equiv. K_3PO_4, DMSO, 50 °C, 65%.

Although we had demonstrated the feasibility of the protocol on the substrate derived from unsubstituted phenylboronic acid, we were concerned with possible functional group compatibility, where necessity of a halogen exchange step under the harsh reaction conditions would preclude the presence of many functional groups on the adjacent substituent R^1. Therefore, in order to allow a broad scope of substrates, an alternative, more robust approach to **1** was needed.

Based on the several literature examples describing the formation of the desired pyridazine-3,6-diamine targets *via* metal-catalysed C-N bond formation reactions using palladium and the corresponding chloro precursors,[7] we were encouraged to investigate that approach. However, the major drawbacks of the existing methods were poor yields, limited scope and poor compatibility with aliphatic amines. Notably however, these reactions used catalysts and ligands found early on in the development of cross-coupling methodologies and had not been evaluated using a more modern catalytic approach. We were determined therefore, to investigate the possibility of introducing a range of primary amines to the electron-rich, substituted pyridazine core by utilising catalytic systems recently published by Buchwald and co-workers.[8] Tentative experiments revealed that a method based on the 'first generation' Brettphos precatalyst[9] was a favourable means to functionalise chloropyridazines such as **5** to give the desired structures represented by **1**.

In order to account for the potentially competitive side reactions arising from the 'free' NH_2 group in **5** we had initially prepared its formamidine derivative **8**. This was felt to be a necessary precaution, based on numerous literature examples for palladium catalysed couplings involving aminopyridazines.[10] With the suitably elaborated substrate **8** we proceeded to the coupling step using the favoured reaction conditions; 5 mol% BrettPhos ligand, 5 mol% BrettPhos precatalyst, 1.5 equiv. primary amine and 2.4 equiv. of 1.0 M LHMDS in THF, which was then heated to 60 °C. This method afforded the desired product **9**, which after final deprotection delivered **7** in very good 75% overall yield (Scheme 2).

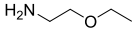
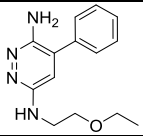
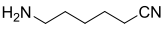
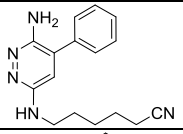
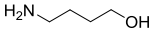
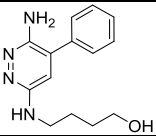
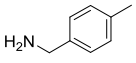
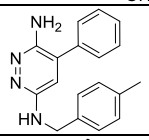
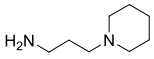
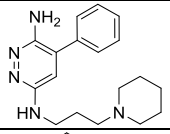
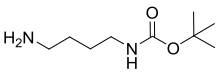
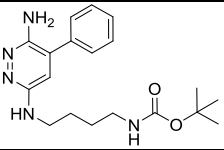
However, it seemed reasonable to hypothesise that the reactivity of the NH_2 group in structures such as **5** could be moderated due to factors such as sterics and electronics from the neighbouring aryl ring. Crucially, following further investigations, we found that 'unprotected' chloropyridazine **5** could be directly converted to target **7** in a single step (step iv in Scheme 2) using the same BrettPhos precatalyst system and conditions employed for the protected derivative **8**. The direct conversion of **5** to **7** was achieved in excellent yield (83%) with no side-products arising from reaction of the unprotected NH_2 functionality.

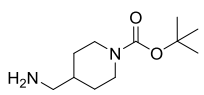
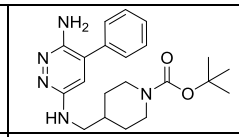
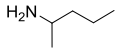
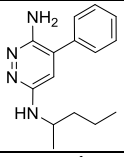
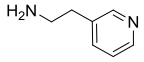
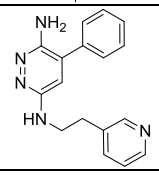


Scheme 2. Reaction conditions: (i) DMF dimethyl acetal, toluene, reflux, 99% (ii) 1.5 equiv. 2-ethoxyethanamine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS, 60 °C (iii) aq. HCl, MeOH, room temp (75% 2 steps). (iv) 1.5 equiv. 2-ethoxyethanamine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS, 60 °C, 83%.

Encouraged by this result, we decided to proceed with an investigation of the scope of this transformation and employed a selection of primary amines with chloropyridazine **5**, under the same palladium catalysed conditions. Results with isolated yields are summarised in Table 1. Functional groups such as ether (entry 1, 83%), nitrile (entry 2, 70%) and alcohol (entry 3, 73%) were well tolerated, as was 4-methylbenzylamine (entry 4, 85%) and a tertiary amine (entry 5, 83%). No desired product was observed for the BOC protected primary amine (entry 6) but moderate yields were obtained for a similarly protected secondary amine (entry 7, 63%) and the hindered 2-methylbutylamine (entry 8, 60%).

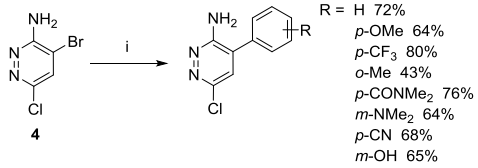
Table 1
Assessment of scope for primary amines

Entry	Amine	Product	Yield (%)
1			83
2			70
3			73[a]
4			85
5			83
6			0[a]

7			**63**
8			**60**
9			**89**

Conditions: 1.5 equiv. amine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS. [a] 3.4 equiv. LHMDS

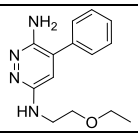
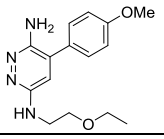
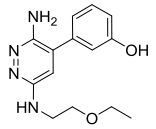
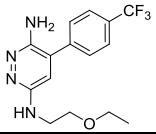
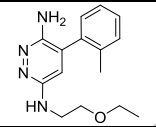
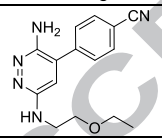
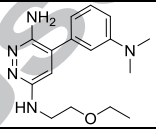
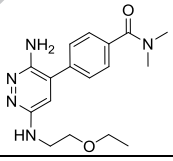
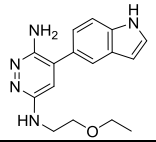
To further assess the functional group tolerance of this method, a range of substituents on the aryl ring were then introduced *via* use of the appropriate boronic acid in the initial Suzuki step. This resulted in good yields of the chloropyridazine precursors (Scheme 3).



Scheme 3. Reaction conditions: (i) 1.03 equiv. $ArB(OH)_2$, $Pd(dppf)Cl_2.CH_2Cl_2$ (10 mol%), 2 equiv. Na_2CO_3, aq. dioxane, reflux. (1H-indol-5-yl)boronic acid gave a yield of 74%

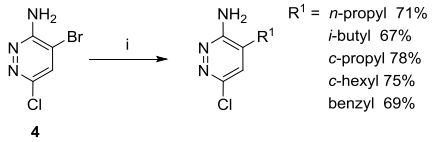
2-Ethoxyethanamine was selected as the model system amine which was used to generate a series of functionalised pyridazine-3,6-diamines (Table 2). Yields for these various, aryl-ring substituted analogues ranged from 42% to 93% with functional groups such as arylether (entry 2, 80%), phenol (entry 3, 93%) and trifluoromethyl (entry 4, 88%) all being very well tolerated. Similarly, the hindered *o*-tolyl example gave a pleasing 81% yield (entry 5) and respectable yields were also obtained for nitrile (entry 6, 65%) and an *N,N*-dimethylaniline (entry 7, 61%). However, the recovery from an amide was low (entry 8, 42%), which was found to be due to a competing 'transamination' reaction at the amide carbonyl centre. Finally, we investigated the use of an indole as shown in entry 9 and were pleased to obtain a 75% yield for this heterocycle.

Table 2
Assessment of scope for aryl functionality

Entry	Product	Yield (%)
1		83
2		80
3		93[a]
4		88
5		81
6		65
7		61
8		42
9		75[a]

Conditions: 1.5 equiv. 2-ethoxyethanamine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS, 60 °C. [a] 3.4 equiv. LHMDS

In order to extend the scope for substituent R^1 we then turned our attention to the analogous alkyl substituted structures. We found that it was possible to treat 4-bromo-6-chloro-3-pyridazinamine **4** under Negishi conditions with the appropriate alkylzinc halide in order to selectively introduce various alkyl groups in good yields (Scheme 4).[11]

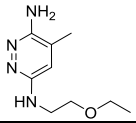
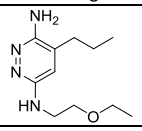
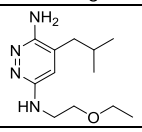
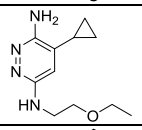
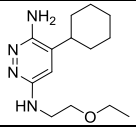
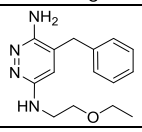


Scheme 4. Reaction conditions: (i) 3 equiv. R^1ZnBr, $Pd(PPh_3)_2Cl_2$ (10 mol%), THF, room temp.

The resultant intermediates were carried through using the same BrettPhos catalytic system as previously described (Table 3). All alkyl examples worked well, apart from the benzyl substrate (entry 6) which gave a low yield of 14%.

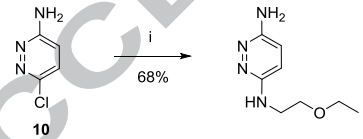
Table 3
Assessment of scope for alkyl substituents

Entry	Product	Yield (%)

1		81
2		70
3		72
4		86
5		64
6		14

Conditions: 1.5 equiv. 2-ethoxyethanamine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS, 60 °C.

Of particular note was the 81% yield for the analogue containing the methyl group (Entry 1, Table 3), the smallest of the R^1 substituents investigated. The transformations shown in Scheme 2 and discussed earlier, had led us to speculate that the unreactive nature of the pyradizine 'NH_2' in these reactions could be due to steric hindrance from R^1 (thus negating the need for the formamidine protecting group shown in Scheme 2). However, the high yield obtained for the methyl substituent in Table 3 suggested that steric hindrance was not a significant factor. Accordingly, we found that we were also able to extend this chemistry to the corresponding unsubstituted (R^1 = H) analogues. 6-Chloro-3-pyridazinamine **10**, for example, gave a respectable 68% yield with 2-ethoxyethanamine under the same conditions (Scheme 5).



Scheme 5. Reaction conditions: (i) 1.5 equiv. 2-ethoxyethanamine, BrettPhos (5 mol%), BrettPhos precatalyst (5 mol%), 2.4 equiv. LHMDS, 60 °C

In summary, we have reported a convenient and facile synthetic approach for accessing a desirable medicinal chemistry scaffold based on 4-aryl and alkyl substituted, N^6-alkylated pyridazine-3,6-diamines. This methodology makes use of selective Suzuki and Negishi transformations using a low-cost, commercially available starting material. Introduction of the desired primary amines was achieved *via* a Buchwald protocol with BrettPhos precatalyst on challenging and previously unexplored pyridazine structures. Moreover, no additional protecting group strategy was required to aid the desired selectivity.

Acknowledgments

We would like to thank Jamie Scott for discussions and also Paul Davey, Scott Boyd, Marta Wylot, Eva Lenz and Steve Glossop for analytical support.

Supplementary Data

Supplementary material (experimental procedures and characterization data, including ^{1}H NMR, ^{13}C NMR spectra) for all table compounds and 'chloro-precursors' associated with this article can be found in the online version.

References

1. See, for example; (a) Khalil, N. A.; Ahmed, E. M.; Mohamed, K. O.; Nissan, Y. M.; Zaitone, S. A. *Bioorg. Med. Chem.* **2014**, *22*, 2080-2089; (b) Abouzid, K. A. M.; Khalil, N. A.; Ahmed, E. M.; Mohamed, K. O. *Arch. Pharm. Res.* **2013**, *36*, 41-50; (c) Yang, S.; Kuo, G.; Gaul, M. D.; Rano, T. A. WO Patent 2013/085957; *Chem. Abstr.* **2013**, *159*, 118568.
2. Semeraro, C.; Dorigotti, L.; Banfi, S.; Carpi. C. *J. Cardiovasc. Pharm.* **1981**, *3*, 455-467.
3. (a) Almario, G. A.; Barrague, M.; Burnier, P.; Enguehard, C.; Gao, Z.; George, P.; Gueiffier, A.; Li, A. T.; Puech, F.; Vaz, R.; Zhao, Q. WO Patent 2009/016286; *Chem. Abstr.* **2009**, *150*, 168375; (b) Zoller, G.; Strobel, H.; Will, D. W.; Wohlfart, P. WO Patent 2008/104279; *Chem. Abstr.* **2008**, *149*, 307879; (c) Falco, J. L.; Palomer, A.; Guglietta, A. WO Patent 2007/110437; *Chem. Abstr.* **2007**, *147*, 406830.
4. (a) Biagetti, M.; Contini, S. A.; Genski, T.; Guery, S.; Leslie, C. P.; Mazzali, A.; Pizzi, D. A.; Sabbatini, F. M.; Seri, C. WO Patent 2009/095377; *Chem. Abstr.* **2009**, *151*, 245649; (b) Bouchain, G.; Delorme, D.; Frechette, S.; Gaudette, F.; Isakovic, L.; Leit, S.; Moradei, O.; Paquin, I.; Raeppel, S.; Vaisburg, A.; Zhou, Z. WO Patent 2005/092899; *Chem. Abstr.* **2005**, *143*, 367317.
5. (a) Xing, L.; Ziener, U.; Sutherland, T. C.; Cuccia, L. A. *Chem. Commun.* **2005**, 5751-5753; (b) Gschwend, H. W.; Kodumuru, V.; Liu, S.; Kamboj, R. U.S. Patent 8148378; *Chem. Abstr.* **2012**, *156*, 477720.
6. Bethel, P. A.; Roberts, B.; Bailey, A. *Tetrahedron Lett.* **2014**, *55*, 5186-5190.
7. (a) Blench, T.; Goodacre, S.; Lai, Y.; Liang, Y.; Macleod, C.; Magnuson, S.; Tsui, V.; Williams, K.; Zhang, B. WO Patent 2012/066061; *Chem. Abstr.* **2012**, *157*, 12801; (b) Currie, K. S.; Wang, X.; Young, W. B. WO Patent 2012/031004; *Chem. Abstr.* **2012**, *156*, 363058; (c) Cho, Y. S.; Borland, M.; Brain, C.; Chen, C. H.; Cheng, H.; Chopra, R.; Chung, K.; Groarke, J.; He, G.; Hou, Y.; Kim, S.; Kovats, S.; Lu, Y.; O'Reilly, M.; Shen, J.; Smith, T.; Trakshel, G.; Vogtle, M.; Xu, M.; Xu, M.; Sung, M. J. *J. Med. Chem.* **2010**, *53*, 7938-7957.
8. Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.*, **2011**, *2*, 57.
9. BrettPhos first generation precatalyst; Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′, 6′-triisopropyl-1,1′-biphenyl][2-(2-aminoethyl)phenyl]palladium(II). CAS 1148148-01-9
10. See, for example; (a) Wagner, P.; Bollenbach, M.; Doebelin, C.; Bihel, F.; Bourguignon, J.; Salome, C.; Schmitt, M. *Green Chem.* **2014**, *16*, 4170-4178; (b) Hu, C. H.; Qiao, J. X.; Han, Y.; Wang, T. C.; Hua, J.; Price, L. A.; Wu, Q.; Shen, H.; Huang, C. S.; Rehfuss, R.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2481-2485; (c) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260-264.
11. 6-Chloro-4-methylpyridazin-3-amine precursor was purchased from Sigma Aldrich.