Bioorganic & Medicinal Chemistry Letters 19 (2009) 1879–1882

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Syntheses of novel 2,3-diaryl-substituted 5-cyano-4-azaindoles exhibiting c-Met inhibition activity

Hannes Koolman [b,*], Timo Heinrich [a], Henning Böttcher [a], Wilfried Rautenberg [a], Michael Reggelin [b]

[a] Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
[b] Clemens-Schöpf Institute of Organic Chemistry and Biochemistry, Technical University of Darmstadt, Petersenstrasse 22, 64287 Darmstadt, Germany

ARTICLE INFO

Article history:
Received 15 January 2009
Revised 18 February 2009
Accepted 18 February 2009
Available online 21 February 2009

Keywords:
Kinase inhibitor
c-Met
4-Azaindole

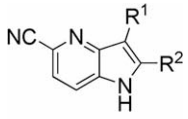
ABSTRACT

Herein we report the syntheses of 2,3-diaryl-substituted pyrrolo[3,2-*b*]pyridine-5-carbonitriles via a one-pot 5-*endo*-*dig*-cyclization/protection reaction followed by palladium catalyzed arylation. In addition, a complementary synthesis route employing Larock methodology is applied to efficiently explore further aryl moieties in the 2-position. The novel compounds' expedient c-Met receptor tyrosine kinase inhibition activity is discussed.

The hepatocyte growth factor (HGF) receptor, also known as mesenchymal–epithelial transition factor (c-Met), is a receptor tyrosine kinase (RTK) present in both normal and malignant cells.[1] The main biological effects upon its signaling pathway activation comprise promotion of tissue regeneration, angiogenesis, and enhanced cell motility.[2] c-Met is known to be over-expressed and mutated in a variety of human cancer types.[3] Thus, signal transduction through the activation of the c-Met receptor is accountable for proliferation, scattering, invasiveness and metastasis of tumor cells. On this account, small molecule inhibitors, preventing receptor autophosphorylation and recruitment of the downstream effectors of c-Met, are of current interest.[4]

Currently, there are several ATP-competitive c-Met kinase inhibitors known, based on different scaffolds.[5] Recent developments feature 7-azaindoles,[6] aminopyridines[6] and triazolopyridazines[7] with high potency and selectivity for c-Met.

As part of our studies towards aromatically substituted azaindoles as kinase inhibitors, the rarely used core structure of the 4-azaindoles in combination with diaryl substitution in the 2- and 3-position attracted our attention.[8,9] At present, this structure is unknown as an inhibitor of c-Met and 5-cyano-2,3-diaryl-4-azaindoles (**1**) in particular have not been previously described as kinase inhibitors. By analogy to known compounds,[8] these pyrrolopyridines are anticipated to offer kinase inhibiting potential.



1

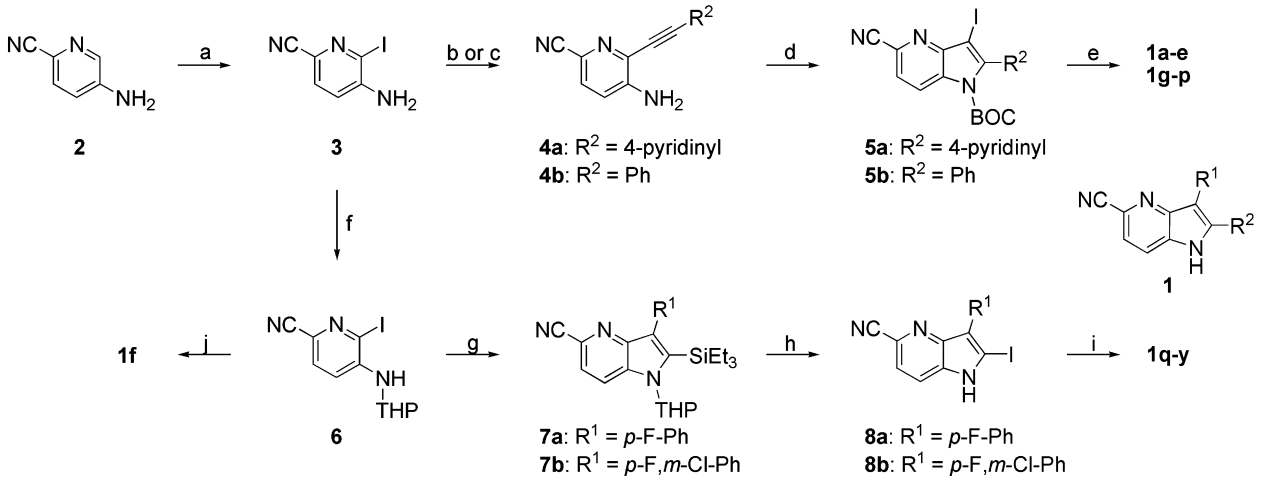
For the full syntheses of azaindoles a growing number of approaches are known, heavily depending on the desired substitution pattern.[10] Recently, Cacchi et al. transferred their highly versatile methodology for the assembly of 2,3-diaryl-substituted indoles[11] onto 4- and 7-azaindoles.[9] This methodology comprises the reaction of 2-alkynyl-3-trifluoroacetamidopyridines with arylbromides and -triflates in an aminopalladation-reductive elimination procedure. However, in our hands, this approach failed to yield the desired 5-cyano-substituted azaindoles due to loss of the trifluoroacetate protecting group under the reaction conditions.[12] Therefore a strategy based upon base-induced cyclization of *o*-aminoalkynylpyridines was employed (Scheme 1).

Silver(I)-assisted electrophilic aromatic iodination of commercially available 5-aminopicolinonitrile **2** gave the mono-iodinated intermediate **3** in 79% yield. The cyclization precursor **4a** could be obtained under Sonogashira-like alkynylation conditions in moderate yield (66%).[13]

Azaindoles **5** were synthesized by subsequent base-induced 5-*endo*-*dig* cyclization in NMP,[14] direct addition of *N*-iodosuccinimide and BOC-anhydride, leading to the protected 3-iodo-4-azaindoles in good yields of 73–83% (see Ref. 15 for an exemplary procedure). These compounds are stable if directly purified via chromatography over neutral aluminum oxide and stored at −20 °C.[16] Arylation in the 3-position was achieved via Suzuki–

* Corresponding author. Tel.: +49 6151 72 5881.
E-mail address: hannes.koolman@merck.de (H. Koolman).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.02.069



Scheme 1. Reagents and conditions: (a) I_2, Ag_2SO_4, EtOH, rt, 79%; (b) 4-ethynylpyridine, Cs_2CO_3, $Pd(dppf)Cl_2$, THF, 50 °C, 66%; (c) 3-phenylpropiolic acid, Na_2CO_3, LiCl, $Pd(dppf)Cl_2$, DMF, 110 °C, 20%; (d) KO^{t}Bu, NMP, 90 °C, then NIS, DCM, 0 °C to RT, then $(BOC)_2O$, DMAP, DCM, 0° to RT, 73–83%; (e) $R^1B(OR)_2$, K_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O 2:1, 85 °C then TFA or ethan. HCl, 60 °C, 25–86%; (f) DHP, $MgBr_2$, THF, 65 °C, quant.; (g) **11a** or **11b**, Na_2CO_3, LiCl, $Pd(dppf)Cl_2$, DMF, 110 °C (h) IPy_2BF_4, TfOH, DCE, 83 °C, 48–66% over two steps (i) $R^2B(OR)_2$, K_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O 2:1, 85 °C, 9–77% (j) **13**, Na_2CO_3, LiCl, $Pd(dppf)Cl_2$, DMF, 110 °C then 1 N HCl, 110 °C, 39%.

Miyaura-coupling with various boronic acids or -esters. The protecting group was quantitatively removed by subsequent acidification of the reaction mixture with TFA or hydrochloric acid to yield the desired 2,3-diaryl-substituted pyrrolo[3,2-*b*]pyridine-5-carbonitriles **1a**–**e** and **1g**–**p**. The BOC-protecting group was indispensable in this step, as unprotected 3-iodo-4-azaindoles failed to undergo efficient Suzuki-type cross-coupling, showing dehalogenation as major side reaction.[17] Thus, employing two one-pot routines we were able to prepare highly decorated 4-azaindoles from quite simple starting materials.

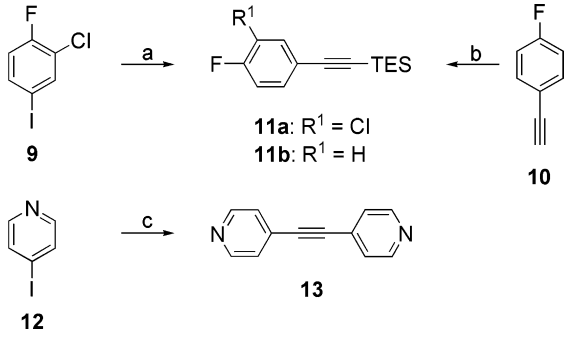
An alternative approach was based upon Larock's indole synthesis. Via this route variable aryl substitution in the 2-position could be efficiently explored. For the key cycloaddition step introduction of an electron donating protecting group was indispensable.[18] Therefore, iodo-aminopyridine **3** was reacted with dihydropyran under Lewis-acid catalysis, yielding **6** quantitatively. The 4-azaindoles **7** were prepared under Larock conditions with triethylsilyl-protected alkynes **11** (vide infra).[19] Thereby, traces of N-deprotected products were generated. This crude product mixture was treated with IPy_2BF_4 in the presence of an excess of triflic acid to convert the TES-group to the corresponding iodides **8**.[20] The THP-group was concurrently removed during this halogenation. Derivatives **1q**–**y** were achieved under standard Suzuki-coupling conditions. It is noteworthy that this coupling works uneventfully without N-protection on the indole. The 2,3-dipyridinyl-derivative **1f** was yielded by Larock-reaction of **6** with symmetrically substituted ethyne **13** and subsequent acidic THP-group removal.

The alkynes **11a**, **11b** and **13**, employed in the Larock reactions with pyridine **6** were prepared according to known procedures (Scheme 2).[21]

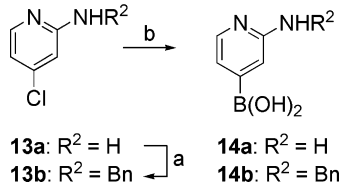
Iodobenzene **9** was converted to **11a** via Sonogashira-coupling with TES-ethyne, whereas 4-ethylnylpyridine and 4-iodopyridine **12** were coupled to ethyne **13**, respectively. Ethynyl-benzene **10** was silylated with TES-chloride after deprotonation with *n*-BuLi, to yield **11b**.

Synthesis of the non-commercially available boronic acids **14a** and **14b** employed in the final synthesis step for the derivatives **1u** and **1v**, respectively, were performed following a procedure published by Buchwald et al. (Scheme 3).[22]

First, the structure activity relation of 4-azaindoles **1a**–**o** with different aryl-substituents in the 3-position is discussed, and their c-Met-kinase inhibition activity is listed in Table 1. The phenyl-



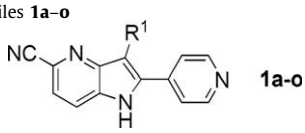
Scheme 2. Reagents and conditions: (a) triethylsilylacetylene, $Pd(PPh_3)_4$, CuI, Et_2NH, 75%; (b) *n*BuLi, TESCl, THF, −78 °C to rt, 86%; (c) 4-ethynylpyridine-hydrochloride, $Pd(PPh_3)_4$, CuI, Et_2NH, 53%.

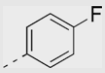
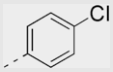
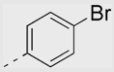
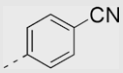
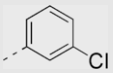
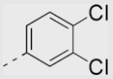
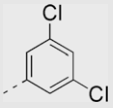
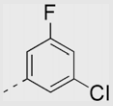
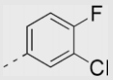
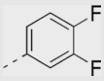
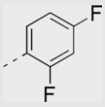
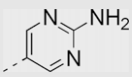
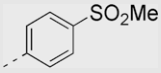


Scheme 3. Reagents and conditions: (a) NaH, BnCl, DMF, 0 °C to rt, 23%; (b) Bis(pincolato)diboron, KOAc, $Pd(dba)_2$, XPhos, dioxane, 110 °C, 95% -quant.

derivative **1a** shows an IC_{50}-value of 2.09 μM, suggesting that lipophilic moieties are preferred as substituents in the 3-position of the 4-azaindole. The activity is maintained with the introduction of a *p*-fluoro substitution (**1b**), but steadily decreases with increasing size of the halogen (**1a**–**d**). Similarly, derivative **1e**, bearing a pseudohalogenic cyano substitution, is significantly less active. The *m*-chloro-derivative **1g**, exhibiting a 50-fold activity increase compared to the phenyl derivative **1a**, indicates that additional halogen substituents are beneficial in this position. In case of the *m*,*m*′-disubstituted derivatives (**1i**, **1j**), the *m*-chloro, *m*′-fluoro-derivative (**1j**) is about 7.5-fold more potent than **1i**. But remarkably, when combining *meta*- and *para*-substitution (**1k**, **1l**) the chloro-substituent (**1k**) is about ninefold superior to the fluoro-derivative (**1l**). However, the *m*-,*p*-dichloro-derivative **1h** is

Table 1
c-Met inhibition activity of the 3-aryl-substitued 2-(pyridin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitriles **1a–o**

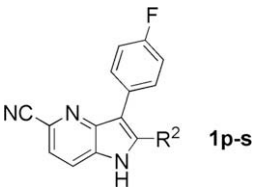


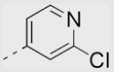
Compounds	R^1	IC_{50}[a]
1a		2.09
1b		1.95[b]
1c		10
1d		>10[c]
1e		>10[c]
1f		na[d]
1g		0.04
1h		>10[c]
1i		2.55
1j		0.34
1k		0.18
1l		1.59
1m		>10[c]
1n		na[d]
1o		na[d]

[a] IC_{50} values represent average values from 2 to 4 measurements, and are defined as the concentration (μM) resulting in 50% inhibition of activity, for assay conditions see Ref. 23.
[b] Exemplary solubility data: (in water at pH 7.4): 1 μg/ml.
[c] Remaining activity >60% at 10 μM
[d] Inactive at 10 μM.

significantly less active. The compounds **1n** and **1o**, bearing an amino-pyrimidinyl and a *p*-methylsulfonyl-phenyl substitution, respectively, are inactive.

Table 2
c-Met inhibition activity of the 2-aryl-substituted 3-(4-fluorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitriles **1p–s**



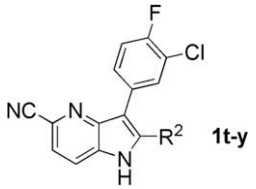
Compounds	R^2	IC_{50}[a]
1p		na[b]
1q		>10[c]
1r		>10[c]
1s		0.33

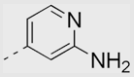
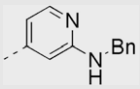
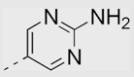
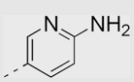
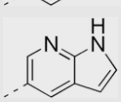
[a] IC_{50} in μM.
[b] Inactive at 10 μM.
[c] Remaining activity >60% at 10 μM.

The potency of **1g** became apparent when the optimization of the 2-aryl-moiety with derivatives of **1b** (see Table 2) and **1k** (see Table 3) was already ongoing.

Comparing the inactive phenyl-derivative **1p** with the above-mentioned pyridine-analog **1b** the pyridine nitrogen is clearly accountable for the μM activity. In case of an influencing *o*-chloro-substituent (**1q**) the activity gain of the pyridine nitrogen

Table 3
c-Met inhibition activity of the 2-aryl-substituted 3-(3-chloro-4-fluorophenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitriles **1t–y**



Compounds	R^2	IC_{50}[a]
1t		>10[b]
1u		0.13
1v		5.57
1w		>10[b]
1x		>10[b]
1y		>10[b]

[a] IC_{50} in μM.
[b] Remaining activity >60% at 10 μM.

is reduced. Derivative **1r**, the pyridine-2-yl-isomer of **1b**,[24] cannot sustain the activity, whereas introduction of a second *meta*-nitrogen (**1s**) obviously compensates this effect. Thus, **1s** is about sixfold more active than the pyridine-4-yl-analog **1b**. In light of published structures[8] this effect is surprising. Obviously, this result cannot be generally extrapolated, because the pyrimidinyl in position 2 together with a *m*-chloro,*p*-fluoro-phenyl-moiety in the 3-position (**1t**, Table 3) reduces activity drastically, revealing subtle structure activity relations.

Compounds **1u** and **1v** are based on **1k**. Comparable derivatization of the pyridine-moiety is known to be beneficial for similar p38-kinase inhibitors.[8] Introduction of a 2-aminopyridin-4-yl-moiety in the 2-position of the azaindole has no effect on activity (**1u**) evidencing that an *o*-amino-substituent is tolerated. Benzyl-substitution in **1v**, however, results in a 30-fold loss of activity compared to **1k**, showing that large lipophilic moieties are not tolerated in this position.

The 2-aminopyridin-3-yl isomer **1x** cannot maintain the activity (compared to **1u**). This observation is consistent with the loss of activity already noticed for the pyridine-3-yl-isomer **1r**. Similarly, the analogs **1w** and **1y** exhibit only weak inhibition activity.

Employing two different protocols based on identical starting material various 2,3-diaryl-substituted 5-cyano-4-azaindoles could be efficiently synthesized. The application of optimized protocols in one-pot procedures enabled a convenient synthesis of highly decorated heterocycles. The compounds showed promising inhibition activity of the c-Met RTK and led to the identification of an inhibitor with an IC_{50} of 40 nM (**1g**).

Elucidation of the compounds' selectivity profiles, particularly discrimination of p38-kinases, is currently under investigation: Preliminary screening of single compounds against a panel of 80 kinases revealed promising selectivities. Further studies comprising improvement of activity and solubility enhancement are currently ongoing in our group.

References and notes

1. Di Renzo, M. F.; Narsimhan, R. P.; Olivero, M.; Bretti, S.; Giordano, S.; Medico, E.; Gaglia, P.; Zara, P.; Comoglio, P. M. *Oncogene* **1996**, *6*, 1997.
2. Morishita, R.; Aoki, M.; Hashiya, N. *Curr. Gene Ther.* **2004**, *4*, 199.
3. Ma, P. C.; Maulik, G.; Christensen, J.; Salgia, R. *Cancer Metastasis Rev.* **2003**, *22*, 309.
4. Peruzzi, B.; Bottaro, D. P. *Clin. Cancer Res.* **2006**, *12*, 3657.
5. Comoglio, P. M.; Giordano, S.; Trusolino, L. *Nat. Rev. Drug. Discovery* **2008**, *7*, 504.
6. (a) Cai, Z. W.; Wei, D.; Schroeder, G. M.; Cornelius, L. A. M.; Kim, K.; Chen, X.-T.; Schmidt, R. J.; Williams, D. K.; Tokarski, J. S.; An, Y.; Sack, J. S.; Manne, V.; Kamath, A.; Zhang, Y.; Marathe, P.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3224; b Hamakima, T.; Nakamura, H.; Tang, J. WO Patent 08049855, 2008.
7. Albrecht, B. K.; Harmange, J.-C.; Bauer, D.; Berry, L.; Bode, C.; Boezio, A. A.; Chen, A.; Choquette, D.; Dussault, I.; Fridrich, C.; Hirai, S.; Hoffman, D.; Larrow, J. F.; Kaplan-Lefko, P.; Lin, J.; Lohman, J.; Long, A. M.; Moriguchi, J.; O'Connor, A.; Potashman, M. H.; Reese, M.; Rex, K.; Siegmund, A.; Shah, K.; Shimanovich, R.; Springer, S. K.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F. *J. Med. Chem.* **2008**, *51*, 2879.
8. 2,3-Diaryl-4-azaindoles are known as p38-MAP-kinase inhibitors: Trejo, A.; Arzeno, H.; Browner, M.; Chanda, S.; Cheng, S.; Comer, D. D.; Dalrymple, S. A.; Dunten, P.; Lafargue, J.; Lovejoy, B.; Freire-Moar, J.; Lim, J.; Mcintosh, J.; Miller, J.; Papp, E.; Reuter, D.; Roberts, R.; Saunders, J.; Song, K.; Villasenor, A.; Warren, S. D.; Welch, M.; Weller, P.; Whiteley, P. E.; Zeng, Lu; Goldstein, D. M. *J. Med. Chem.* **2003**, *46*, 4702.
9. Cacchi, S.; Fabrizi, G.; Parisi, L. M. *J. Comb. Chem.* **2005**, *7*, 510.
10. Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.
11. Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.
12. Cacchi, S. et al. reported similar instability of *o*-acetoxyalkynylpyridines containing strongly electron-withdrawing substituents in the pyridine ring. Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409.
13. The phenyl-derivative **4b** was obtained as a side product of a Larock reaction of iodoaminopyridine **2** and 3-phenylpropiolic acid in 20% yield.
14. Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.
15. *Exemplary synthesis procedure* (**1g**): 331 mg (1.50 mmol) of **4a** were Schlenk tube-dried and were dissolved in NMP (15 ml) under nitrogen. 287 mg (2.55 mmol) KO^{t}Bu were added and the mixture was stirred for 4 h at 90 °C, then cooled to 0 °C and a solution of 507 mg (2.25 mmol) NIS in NMP (10 ml) added drop wise. After 1 h at room temperature, a solution of 1.64 g (7.52 mmol) $(BOC)_2O$ and 183 mg (1.50 mmol) DMAP in NMP (5 ml) was added at 0 °C. After 1 h at 0 °C the reaction mixture was diluted with water (250 ml) and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried and evaporated. After flash-chromatography over neutral Al_2O_3 (eluent: ethyl acetate/cyclohexane 9:1) 563 mg (1.26 mmol, 83%) tert-butyl 5-cyano-3-iodo-2-(pyridin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridin-1-carboxylat **5a** was yielded as white solid. Mp 126–129 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (m, 2H), 8.60 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.53 (m, 2H), 1.25 (s, 9H). ESI-MS: *m/z*: 447 ($[M+H]^+$), 347 ($[M-BOC]^+$). Anal. Calcd for $C_{18}H_{15}IN_4O_2$: C, 48.45; H, 3.39; N, 12.56. Found: C, 49.00; H, 3.80; N, 12.00. 223 mg (0.50 mmol) of **5a**, 117 mg (0.75 mmol) of 3-chlorophenylboronic acid and 207 mg (1.50 mmol) of K_2CO_3 were dissolved in 7.5 ml of DME/H_2O 2:1 in a capped vial. After degassing employing ultrasound under nitrogen 20.4 mg (0.025 mmol) of $Pd(dppf)Cl_2xCH_2Cl_2$ were added and the reaction mixture stirred at 80 °C for 6 h. Then 5 ml of TFA were added and the mixture stirred at 60 °C for 15 h, set to pH 12 using dil NaOH and extracted with ethylacetate. The combined organic phases were dried, evaporated and purified via flash-chromatography (eluent: ethyl acetate to ethyl acetate/methanol 95:5) to yield 95.0 mg (0.287 mmol) of 3-(3-chlorophenyl)-2-(pyridin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine-5-carbonitrile **1g** as a beige solid. Mp 267 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.71 (s, 1H), 8.67 (d, J = 5.6 Hz, 2H), 8.00 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.55 (m, 1H), 7.51–7.36 (m, 5H). APCI-MS: *m/z* (%): 331 (100, $[M+H]^+$).
16. At room temperature under atmosphere compounds **5** show dehalogenation as major decomposition reaction.
17. Without BOC-protection, product yields only less than 15% could be achieved under various reaction conditions. Similar observations for Suzuki-couplings in the 3-position of pyrroles are reported in the literature: Handy, S. T.; Bregman, H.; Lewis, J.; Zhang, X.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 427. and citations within.
18. During our studies towards the synthesis of electron-deficient 4- and 7-azaindoles via Larock reaction the tetrahydropyranyl-moiety was found to be highly enhancing reactivity of the aminopyridine. Results will be published elsewhere.
19. The TES-group was used instead of TMS-protection, offering superior stability during the Larock-reaction.
20. Barluenga, J.; Gonzales, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asencio, G. *J. Org. Chem.* **1993**, *58*, 2058.
21. Larock, C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652; Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11380.
22. Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359.
23. The assay is based on procedures described in: Hays, J. L.; Watowich, S. J. *J. Biol. Chem.* **2003**, *278*, 27456; Wang, X.; Le, P.; Liang, C.; Chan, J.; Kiewlich, D.; Miller, T. *Mol. Cancer Ther.* **2003**, *2*, 1085.
24. Synthesis of the 1-pyridinyl-isomer of **1r** failed, leading to a complex reaction mixture.